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THE ANAEROBIC NONHEMOLYTIC STREPTOCOCCI IN SURGICAL INFECTIONS ON A GENERAL SURGICAL SERVICE

WILLIAM ROBERTS SANDUSKY, M.D., EDWIN J. PULASKI, M.D.,
BALBINA A. JOHNSON, A.B., and FRANK L. MELENEY, M.D., F.A.C.S., New York, New York

IMPROVEMENTS in anaerobic bacteriological technique and the emphasis in recent years on the employment of anaerobic as well as aerobic cultures in diagnostic work have increased the number of isolations of anaerobic micro-organisms and as a result the number of reports on studies of infections due to these organisms. The Clostridia have received the greatest attention and their biological, immunological, and cultural characteristics are well known. Less attention has been paid the anaerobic Gram negative bacilli and the anaerobic cocci. The latter group of organisms, while extensively reported in European literature (73), have received considerably less attention in the American literature and, save for their rôle in puerperal infections, knowledge concerning them is not widely disseminated.

This paper will be concerned only with the anaerobic nonhemolytic streptococci, and its purpose is to review critically the literature regarding this group of organisms and to present 170 cases of surgical lesions from which the anaerobic nonhemolytic streptococci were recovered.

From the Bacteriological Research Laboratory of the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Surgical Service of the Presbyterian Hospital.

REVIEW OF THE LITERATURE

The first isolation of an anaerobic nonhemolytic streptococcus is generally credited to Veillon, who in 1893 described under the name of Micrococcus foetidus a strictly anaerobic coccus growing in short chains and producing gas and a fetid odor in cultures. This organism had been isolated in pure culture from a case of suppurative bartholinitis, and in association with other organisms from a case of Ludwig's angina and a perinephritic abscess.

Since Veillon's report there have appeared in the literature numerous articles, some reporting series of cases, others dealing with isolated observations, on the recovery of anaerobic nonhemolytic streptococci, in pure culture and in association with other organisms, from various lesions as well as healthy body cavities and surfaces. A list of these sources, tabulated on the basis of the normal habitat of the organism in the human body is presented in Table I. This same grouping has been adhered to in the review of the literature which follows.

TABLE I.—THE NORMAL HABITAT, SOURCES OF INFECTION AND DISEASES FROM WHICH THE ANAEROBIC NONHEMOLYTIC STREPTOCOCCI HAVE BEEN RECOVERED

Oral cavity—
Normal flora. Normal sinuses. Gingivitis. Ulcerative stomatitis. Dental caries. Tooth granulomas. Alveolar abscesses. Retropharyngeal abscesses. Tonsillitis. Deep cervical abscesses. Ludwig's angina. Infected carcinoma. Sinusitis. Mastoiditis. Otitis media. Leptomeningitis. Cerebral abscess. Aspiration pneumonia. Pulmonary gangrene. Lung abscess. Empyema thoracis. Septicemia. Tooth wounds.

Gastrointestinal tract—
Normal intestinal flora. Acute and chronic cholecystitis. Liver abscesses. Acute appendicitis. Appendiceal abscesses. Acute peritonitis. Putrid enteritis. Anorectal infections. Wound infections.

Female genitourinary tract—
Normal flora. Foul lochia. Endometritis. Parametritis. Cervicitis. Bartholinitis. Salpingitis. Tubo-ovarian abscesses. Peritonitis. Infected carcinoma. Septicemia. Metastatic abscesses. Thrombophlebitis. Septic abortion. Bacterial endocarditis. Pulmonary gangrene.

Miscellaneous
Accidental wounds. War wounds. Gas gangrene. Postoperative wound infections. Intertrigo. Periurethral suppurations. Pyonephrosis. Perinephritic abscesses. Osteomyelitis. Synergistic gangrene.

The oral cavity. The bacteria present in the mouth are subjected to great variation both in number and in kind. The amount of detritus, the presence of mucus and organic matter all favor the growth of bacteria and the production of inflammatory conditions of the gums, tonsils, and pharynx. Of the great number of different organisms which abound in the mouth and saliva, among the commonest are the Gram positive cocci, including the anaerobic nonhemolytic streptococcus. Lewkowicz (1901) isolated from the mouths of sucklings an extremely minute streptococcus growing only under strictly anaerobic conditions and producing neither gas nor odor in artificial media. Since this report other observers have confirmed the almost constant presence of anaerobic nonhemolytic streptococci in the human mouth as part of its normal flora. The percentage of positive cultures, low in infants, increases with the appearance of teeth (5). These organisms have been cultured from pyorrheic gums (25, 47, 63), from the lesions of ulcerative stomatitis (43), from tooth sockets (53) after extraction and from alveolar abscesses (31, 67). Such foci may become a source of severe infection elsewhere. A badly abscessed tooth may occasion a deep cervical abscess or a Ludwig's angina. Carcinomas connected with the oral cavity sometimes become infected with these organisms. Recently Freeman has reported 13 positive cultures which were obtained in 18 cases. Anaerobic nonhemolytic streptococci have been isolated also from normal (67) and diseased paranasal sinuses (39).

Brisotto and Schottmueller (59) called attention to the presence of these organisms in the foul smelling pus of chronic otitis media. The mastoid process may become affected, and mastoiditis and lateral sinus thrombosis with positive blood cultures have been reported. Brisotto pointed out that infection with these organisms may invade the cranial cavity with the development of localized abscesses or diffuse purulent leptomeningitis. He believed the anaerobic streptococci in these instances to be of buccal origin. Meleney (45) has also reported chronic brain abscesses due to anaerobic nonhemolytic streptococci. Meningitis due to these organisms has been observed by other authors (39), as has cerebral abscess (26) of hematogenous origin.

Frankel, Kissling (35), Reye, and Weyrich have made significant contributions to our knowledge of septicemias secondary to infected tonsils. Instances of anaerobic nonhemolytic streptococci invading the blood stream following peritonsillar and retropharyngeal abscess and tonsillectomy have been assembled. It has been shown that the organisms invade thrombosed veins, setting up a thrombophlebitis. The dislodged thrombi are transmitted to the brain, heart valves, or lungs. The outcome in a high proportion of the cases is fatal.

Human bites and lacerations produced when teeth are struck, frequently result in very serious infections, especially when the hand is the injured member. The resulting infection is marked by an intense edema, a foul discharge, and a gangrenous wound, which may involve bones and joints. In a review of the bacteriology of human bite infection, Barnes and Bibby were able to collect only 10 papers which contained accounts of cultural studies and among them were only 6 which had anaerobic as well as aerobic cultures. In all of these, anaerobic Gram positive cocci were uniformly

present, frequently in combination with spirochetes and fusiform bacilli. The most serious human bite infections, according to Jaeger, are due to anaerobic streptococci, and he states that the course of the infection is not controlled until the anaerobes are eradicated. Meleney (44) believes that all serious human bite infections are due to the synergistic action of anaerobic nonhemolytic streptococci with the fusiform bacilli and spirochetes, the combination of these organisms being much more virulent than pure cultures of the same organisms.

The bacteria commonly found in the oral cavity are capable of invading the lungs and producing varying degrees of tissue destruction and ultimately abscess formation. Guillemot in 1898 (27), first called attention to the presence of anaerobic nonhemolytic streptococci in putrid lung abscesses and other pleuropulmonary diseases. Since this account these organisms have been reported (13, 19, 25, 26, 28, 34, 39, 54, 55, 67, 75, 76), in connection with cases of pneumonitis, pulmonary gangrene, lung abscess, and empyema. Kissling (34) pointed out that the aspiration of these organisms with blood, mucus, or fragments of tissue in the course of tonsillectomy or extraction of teeth may give rise to lung abscess. Postpneumonic abscesses sometimes yield anaerobic streptococci. While not definitely proved, these are probably due to the invasion of the devitalized or infected areas of lung by micro-organisms from the mouth. Cultures of pulmonary abscesses present the most varied types of bacterial findings. Smith believes that the fuso-spirochetal group of anaerobic organisms are probably the etiological agents. Kissling (34), on the other hand, concludes from his studies that the cause of pulmonary abscess and gangrene is the anaerobic nonhemolytic streptococcus and that the spirochetes and fusiform bacilli which are frequently found in connection with this organism are saprophytes, having been carried into the lung substance in the process of aspiration, where they find an environment favorable to their existence and multiply in great numbers. Pilot and Davis state "it would seem that the streptococcus or other pyogens affect the [lung] tissue first, preparing the soil for the growth of the anaerobes [fuso-spirochetal]." Thus far we have been concerned with the anaerobic nonhemolytic streptococcus in relation to pulmonary abscess of the spiration type. We shall later see that it plays a similar rôle in the embolic infections.

The gastrointestinal tract. Jacobsen in 1908 was probably the first to mention the isolation of anaerobic nonhemolytic streptococci from the normal intestinal tract. He reports finding them in the stools of newborn infants. In 1926, Tissier was able to isolate from cases of putrid enteritis anaerobic nonhemolytic streptococci which he described as a new species under the name Coccus lanceolatus anaerobius. While undoubtedly the anaerobic streptococci are normal inhabitants of the gastrointestinal tract, it is possible that some may be introduced from the mouth in the process of swallowing saliva. McDonald, Henthorne, and Thompson reported a perforated duodenal ulcer which was followed 2½ months after surgical closure by a subdiaphragmatic abscess, empyema thoracis, and multiple abscess of the liver. Anaerobic nonhemolytic streptococci were obtained in pure culture from the latter. Presumably the organisms originated in the spilled duodenal contents. Gilbert and Lippmann (23) recovered these organisms in 25 per cent of their cases of suppurative cholecystitis. There is an abundance of literature on the bacteriology of acute appendicitis, and numerous investigators (1, 2, 9, 30, 39, 46, 74) have shown that the anaerobic nonhemolytic streptococcus forms part of the bacterial flora of acute suppurative, gangrenous, and perforative appendicitis, with peritonitis or abscess. In this connection it is noteworthy that the commonly held belief that Escherichia coli is the cause of the foul odor of pus in appendiceal peritonitis has been refuted by several observers (2, 9, 30). Certain anaerobic organisms, among which are the anaerobic nonhemolytic streptococci, are responsible for this foul odor. Terrell reported an interesting case of infection on a superficial anal fistula which spread rapidly into the deep subcutaneous tissues of the skin over the trunk and extremities. From the areas of drainage established by numerous surgical incisions, anaerobic strep-

tococci and Escherichia coli were grown out consistently.

The female genital tract. The relationship of the anaerobic nonhemolytic streptococcus to puerperal infections has been well presented in the articles of Schottmueller (59, 60), Schwarz and Dieckmann, Harris and J. H. Brown, Colebrook, T. K. Brown, and Watson. A résumé of the rôle of this organism in puerperal infections is repeated here for the sake of general interest.

Two years after Veillon's report, Kroenig and Menge (48) first independently and later in collaboration (49) described a strictly anaerobic streptococcus which had been isolated from the vagina in pregnancy and in puerperal infection, as well as from cases of parametrial suppuration and peritonitis. In 1905 Natvig recovered from the vagina in pregnancy anaerobic streptococci which produced gas and foul odor in artificial media. He concluded that all strains of anaerobic streptococci, because of their similarity in producing gas and odor should be placed in a single group, to which he gave the name Streptococcus anaerobius. He was apparently unaware of the strain isolated from the mouths of sucklings by Lewkowicz 4 years previously which produced neither gas nor odor in artificial media. There then followed reports by numerous observers dealing with the recovery of anaerobic nonhemolytic streptococci from the normal vagina and from various puerperal states and infections. Suggestions were made by some that these organisms were the cause of puerperal fever. It was not, however, until 1910 when Schottmueller (59) isolated from puerperal infections a strain called by him Streptococcus putridus, that interest in the anaerobic streptococcus as a causative agent of these infections received real acceleration. This worker then and subsequently (60) has emphasized the definite relationship of the anaerobic nonhemolytic streptococcus to puerperal infections. He described a series of cases, chiefly following abortions, characterized by foul lochia, high intermittent fever, chills, rapid pulse, and locally, thrombosis of the pelvic veins. He stated that once the organism (Streptococcus putridus) was able to invade the tissues it became virulent. Detached thrombi were able to establish metastatic infections in other organs, particularly the lungs and pleura. His observations have since been confirmed and extended by other workers. Many phases of puerperal infection have been subjected to extensive investigation, from which we have learned certain facts. These are as follows: nonhemolytic anaerobic streptococci exist in the normal vagina (10, 11, 64, 77), and under ordinary circumstances are nonpathogenic. Under certain conditions, however, they may acquire virulence and may cause mild infections characterized by profuse fetid lochia, low grade fever of short duration, and a soft, tender, subinvoluted uterus. From such mild infections more serious ones may ensue. There may be extension to the peritoneal cavity with the production of peritonitis. There may be thrombophlebitis of the pelvic veins and a remitting fever lasting for considerable time. The organisms may invade the blood stream and produce a true septicemia. Infarcts arising from thrombophlebitis of the pelvic veins may establish metastatic infections in the lung, leading to pulmonary gangrene or suppuration. Bacterial endocarditis has been observed. A certain number of these puerperal infections have gone on to fatal termination. Some observers (50, 71) have reported the detection of anaerobic streptococci with other anaerobes in infections superimposed upon carcinoma of the cervix and fundus of the uterus. In 25 cases of chronic tubo-ovarian abscess Altemeier (3) found the anaerobic streptococcus in pure or in mixed cultures by far the most frequent organism.

Miscellaneous sources. There are numerous infections, other than those already mentioned, from which anaerobic nonhemolytic streptococci have been recovered. Greater knowledge concerning the mode of contamination in each instance would in all probability lead to an accurate determination of the original source for the organisms and a more adequate grouping.

Those infections apparently arising from the skin are an example. Almost any type of micro-organism may be found on the skin surface, the number and varieties depending largely on the body location, environmental

conditions, and opportunity for contamination from various sources. Sussmann, in a study of intertrigo, reports anaerobic nonhemolytic streptococci commonly present and, according to this author, responsible for the foul odor attending the disease. The skin is only one of the many sources for contamination of acute traumatic wounds; however, for the sake of convenience, observations on the bacteriology of such cases will be included in this section. Studying the bacterial flora of acute traumatic wounds, Pulaski, Meleney, and Spaeth examined débrided tissue fragments which included skin, and they recovered anaerobic nonhemolytic streptococci from 13 cases, 6.5 per cent. Cottet (17) and Gerard and Romant have reported the detection of these organisms in war wounds at varying intervals after injury. Three cases of gas gangrene developing in traumatic wounds of civilian practice and war and apparently due to the anaerobic nonhemolytic streptococcus have been described in the literature (40, 62).

An unusual postoperative infection is the progressive bacterial synergistic gangrene recognized as a clinical entity by Meleney (6, 42). This is an excruciatingly painful chronic gangrene of the skin occurring infrequently as a complication of gastrointestinal or thoracic operations and characterized by differentiation into three skin zones: outer brilliant red, middle dusky purple, and inner gangrenous with a central area of granulation tissue. Meleney has demonstrated experimentally that the infection is due to the symbiotic action of a microaerophilic nonhemolytic streptococcus and a hemolytic Staphylococcus aureus. The streptococcus is not strictly anaerobic but is in that group called by Prévot "anaerobes by predilection."

As early as 1900 Cottet (16) in his thesis reported on the recovery of anaerobic streptococci from fetid periurethral suppurations, pyonephrosis, perinephritic abscesses, and other urinary infections. It is only recently, however, that infections of wounds following operations on the urinary tract have been mentioned in the literature. Mathé, reporting such a case, urges careful anaerobic bacteriological studies on all wounds of the urinary tract which resist the usual forms of treatment.

Anaerobic nonhemolytic streptococci in conjunction with other organisms have been grown from the fetid pus of osteomyelitis (38, 52).

CLASSIFICATION

Morphologically the anaerobic nonhemolytic streptococci are not strikingly unlike other varieties. They differ from the aerobic streptococci in their intolerance to oxygen. Gottlieb was able to demonstrate that the presence of oxygen in the media tends to act as a sterilizing agent for these organisms. Other observers (53, 67) have reported that certain strains remain strict anaerobes after as many as 50 to 100 generations.

In the field of classification, Prévot's work (55) is important in that it represents the first serious attempt to classify the anaerobic nonhemolytic streptococci and to group them according to their morphological and biological characteristics. In his original scheme he placed these organisms in 3 groups. In group A were those which produce gas and fetid odor in artificial media. This group includes Streptococcus foetidus (Veillon, 1893), Streptococcus anaerobius (Kroenig, 1895) and Streptoccus putridus (Schottmueller, 1910). Group B contained those which produce neither gas nor odor. Into this fall Streptococcus micros (Lewkowicz, 1901) and Streptococcus intermedius (Prévot, 1925). Group C contained only one organism, Streptococcus evolutus (Graf and Wittneben, 1907) which produces neither gas nor odor and which is an anaerobe by predilection (microaerophilic). Recently Prévot (56) has revised the general grouping, forming two groups instead of three: Group A, to the list given is added Streptococcus lanceolatus (Tissier, 1926) and Group B, which now includes Streptococcus evolutus. The organisms in each group are distinguished from each other by their biological reactions and morphology. The classification is still elaborate and the differentiation is not clear in many instances.

Dissatisfied with the then existing method of classification, and with the hope of arriving at a more adequate one, Colebrook and Hare (15) studied sixty strains of anaerobic streptococci isolated from the blood stream and uteri in cases of puerperal sepsis. They were able

to recognize four chief types based on morphology and colony appearance on horse blood agar. These were referred to as types A, B, C, and D. The former two occurred commonly; the latter two were seldom seen. This classification is open to criticism because of the emphasis and dependence placed on colony appearance as a means of differentiation.

Weiss and Mercado, working with two strains of anaerobic nonhemolytic streptococci, on the basis of protein extract studies, found these organisms sufficiently different in their immunological properties to constitute distinct entities. This seems to represent a proper approach to the problem of classification, but the number of strains studied should be larger to be considered significant.

Recently Stone has reported a study of the biochemical and immunological properties of 26 strains of nonhemolytic anaerobic streptococci isolated from the uterus of parturient and postabortal women. This worker could discern no correlation between any two biological methods of grouping. Nor was it possible to form definite groups from these strains by means of precipitin reactions. He did, however, conclude that certain antigens are present in common and that a study of such antigens may well aid in classifying the organism.

REPORT OF CASES

Bacteriological studies on the cases reported in this paper were made in the Bacteriological Research Laboratory of the Department of Surgery of the College of Physicians and Surgeons, Columbia University. Since July 1, 1939, this laboratory has received for diagnosis all bacteriological specimens from the surgical service of the Presbyterian Hospital and Vanderbilt Clinic. All of the specimens are studied for anaerobic as well as aerobic organisms. The material is inoculated in a 0.2 per cent dextrose cooked beef heart medium, which has been previously boiled and rapidly cooled to expel the oxygen, and is streaked on the surface of two 5 per cent sheep's blood agar plates. One of the plates is incubated under aerobic conditions. The other plate and the broth are incubated anaerobically for 18 hours in an atmosphere of hydrogen in a jar, a modification (45) of the McIntosh and Fildes apparatus being used. No cultures should be discarded until after one week and, unless all morphological forms seen on the Gram stain preparation of the cooked beef heart medium have been recovered and identified, reincubation and replating of this medium is carried out. It has been our experience that those species which grow slowly can be cultivated better on an enriched[1] veal heart infusion agar incubated under anaerobic conditions. Further details of the anaerobic technique used in this laboratory have been reported elsewhere (45). At this point it is well to state the criteria by which these nonhemolytic streptococci were judged to be anaerobes. We have included: (1) those strains which remained strict anaerobes even after being subjected to repeated subcultures on artificial media; (2) those strains which grew as strict anaerobes through the second generation but which, because of a desire for economy in materials and time, were not further subcultured—it is possible that some of these in subsequent generations may have shown microaerophilic tendencies; (3) those strains which were demonstrated to be preferential anaerobes and which would be classified according to Prévot as belonging to the Streptococcus evolutus group.

The services from which this material comes do not include otolaryngological, neurosurgical, urological, obstetrical, or gynecological patients. Of the 170 cases reported only 8 can be considered as belonging to these specialties. The number of cases in this series gains significance, therefore, when it is pointed out that the lesions in such a large proportion represent infections from a general surgical service and include both hospital and ambulatory patients. During the 27 month period, July 1, 1939 through September 30, 1941, the anaerobic nonhemolytic streptococcus has been isolated from 170 different lesions. It occurred 29 times in pure culture, 18 times in association with other anaerobes only, 96 times in association with aerobes only, and in 27 instances was present with both aerobes and other anaerobes.

[1]Enriched by the addition of: 30 c. c. of ascitic fluid, 15 c. c. of blood, 1.5 c. c. of 10 per cent cysteine hydrochloride, and 1.5 c. c. of 20 per cent dextrose to 100 c. c. of a veal heart infusion broth.

The 29 cases from which the anaerobic nonhemolytic streptococcus was isolated in pure culture are listed in Table II. These cases occupy a most important position in our series in that they present very strong evidence in behalf of the pathogenicity of the anaerobic nonhemolytic streptococcus. While it is not our purpose to enter into a detailed description or discussion of the clinical aspects of each of these cases, three groups of lesions and several individual cases are worthy of brief comment.

In numbers perirectal abscess heads the list; there were 9 of these from which this organism was obtained in pure culture. Clinically these were typically represented by an acute abscess situated in the perirectal region and accompanied by considerable pain and tenderness. They contained varying amounts of pus which was usually described as having a foul odor. Upon incision and drainage all save one healed promptly and there appeared to be, save in this instance, no tendency toward chronicity, except when concomitant anal fistulas were demonstrated.

In addition to this group of lesions there were 4 cases of infected pilonidal cyst and 3 of infected sebaceous cyst showing nonhemolytic anaerobic streptococci in pure culture.

The brain abscess case is quite similar to one which has been reported by Cohen (12). It followed pulmonary abscess with a secondary empyema, which was treated surgically at another hospital. This patient died subsequent to drainage of the brain abscess.

One of the cases of empyema is particularly interesting. This occurred in a 43 year old man who had been operated upon 6 years previously for acute appendicitis with perforation and as a sequela had developed chronic phlebitis in the left leg. Shortly before entry he was seized with sharp pleuritic pain. Examination revealed what was considered to be atelectasis and consolidation of the left lower lobe. He improved on sulfapyridine; however, subsequently there developed a localized collection of thick foul smelling green pus from which anaerobic nonhemolytic streptococci were obtained in pure culture on three different occasions. Recovery followed drainage by rib resection.

TABLE II.—TWENTY-NINE CASES FROM WHICH THE ANAEROBIC NONHEMOLYTIC STREPTOCOCCUS WAS ISOLATED IN PURE CULTURE

	Cases
Perirectal abscess	9
Infected pilonidal cyst	4
Infected sebaceous cyst	3
Empyema thoracis	2
Cholecystitis	2
Abscess of thumb	1
Infected branchial cyst	1
Brain abscess	1
Appendiceal abscess	1
Intraperitoneal abscess	1
Liver abscess	1
Pericholecystic abscess	1
Lung abscess	1
Postoperative wound infection	1

The appendiceal abscess case occurred after an appendectomy had been performed nineteen days previously in another hospital. The wound had healed satisfactorily and the patient was ambulatory when the symptoms and signs of an intra-abdominal abscess presented. At operation this proved to be situated in the pelvis, was well walled off, and contained 100 cubic centimeters of thick yellow odorless pus from which anaerobic nonhemolytic streptococci were obtained in pure culture. Prompt recovery followed the operation.

Of the gall bladder cases one occurred in a 59 year old woman who at operation had a distended, acutely inflamed gall bladder filled with white bile and stones. Anaerobic nonhemolytic streptococci were obtained in pure culture from both bile and gall bladder wall.

A case of particular interest is that of a liver abscess, without demonstrable portal of entry which occurred in a 19 year old boy who experienced chills and fever for 4 weeks prior to entry. Uneventful recovery took place following a two stage transthoracic drainage of the abscess.

The lung abscess case occurred secondary to bronchogenic carcinoma, the intra-abdominal abscess case followed leiomyosarcoma of the uterus, and the case of pericholecystic abscess was a complication of acute cholecystitis with perforation of the gall bladder. The postoperative wound infection occurred in a thoracotomy wound following exploration for carcinoma of the esophagus. Among the 4 remaining cases there were no remarkable features other than the bacteriological findings.

TABLE III.—RECORD OF 170 CASES BY GROUPS—MICRO-ORGANISMS ISOLATED

	Number of cases	Anaerobic nonhemolytic streptococcus	Microaerophilic nonhemolytic streptococcus	Clostridium welchii	Spirochetes	Fusiform bacilli	Vibriones	Actinomyces	Bacteroides group	Gram positive cocci anaerobic	Gram positive bacilli anaerobic	Gram negative bacilli anaerobic	Microaerophilic hemolytic streptococcus	Streptococcus hemolyticus	Green streptococcus	Staphylococcus albus	Staphylococcus aureus, nonhemolytic	Staphylococcus aureus hemolyticus	Micrococci	Bacillus subtilis	Diphtheroids	Escherichia coli	Bacillus proteus	Aerobacter aerogenes	Bacillus fecalis alkaligenes	Bacillus pyocyaneus	Gram negative bacilli, unclassified
1. Appendiceal abscess	10	7	3	2											1												
2. Other intra-abdominal abscesses[1]	11	11		1				2			1	2		1								7	6	1			
3. Cholecystitis, acute and chronic	5	4	1														2					1					
4. Peritonitis secondary to appendicitis	8	6	2	2					1		1		1		1		1	1				7			1		
5. Peritonitis, other causes[2]	2	2		2											1							2					
6. Wound infections following gastrointestinal operations	8	7	1	2					1					5	1	2				1	1	4	1		1		1
7. Wound infections following other operations[3]	6	5	1									1		1	2	4	1		1	1							1
8. Abdominal wall abscess	5	5						1	1			1		2		2	1					1	1				
9. Infected pilonidal cyst	13	13		2						1		1	1	3	1	5	3		1			2	1				2
10. Perirectal abscess	28	27	1	3								5	1	3	1	2	1		1			9					1
11. Empyema thoracis	9	9			3					1		2		2		2			1						1		
12. Lung abscess	8	8		6	7	5						1		1	1	1				1							1
13. Brain abscess	1	1																									
14. Infected branchial cyst	1	1																									
15. Paronychia	7	6	1														5	3				1		1			
16. Other hand infections[4]	5	5										1		1	1			2				1					
17. Salpingitis, subacute	1	1												1									1				1
18. Bartholin's abscess	3	3															1	1	1	1	1						
19. Infected sebaceous cyst	7	7													1	1	1			1							
20 Varicose ulcer	3	3												3		1	2					1	1	1			
21. Synergistic gangrene	3	2	1	1												1	1			1	3	1			1		
22. Undermining ulcer	3	3		1										2		1	1										
23. Other chronic ulcers[5]	6	6												2		1	5						1			2	
24. Abscesses, miscellaneous[6]	5	4	1						1			1		1		3									1		
25. Superficial infections, miscellaneous[7]	12	12												1	1		2		1				1				
Total	170	158	12	16	6	10	5	3	4	1	3	15	9	12	34	7	36	20	2	7	8	46	10	5	2	8	9

[1]Subhepatic abscess; liver abscess; pericholecystic abscess; subphrenic abscess; abscess following ileocolectomy; abscess following cholecystectomy; abscess following resection of colon; abscess secondary to leiomyosarcoma of uterus; abscess of unknown etiology (3).

[2]Peritonitis secondary to perforated carcinoma of colon; peritonitis etiology unknown.

[3]Infection around wire hole, clean fracture; wound infection following bone graft; infected wound following arthrotomy; stitch abscess following tenoplasty; wound infection following exploratory laparotomy for carcinoma of the kidney; infection in drain tract following radical mastectomy.

[4]Infection of finger following dog bite; infection of finger following laceration; abscess of thumb, abscess of wrist, abscess of finger.

[5]Posttraumatic ulcer; postirritation ulcer; ulcer secondary to burn; chronic nonspecific ulcers (3).

[6]Abscesses of: axilla; neck; superior maxilla; subperiosteum; submaxillary abscess.

[7]Infection of: burn (2); lip; popliteal space; great toe; amputation stump (3); epithelioma of vulva; carcinoma of breast; axillary granuloma; furuncle of face.

Table III records the 170 cases by groups and indicates all of the organisms isolated in each group. Among these cases there can be found a wide range of lesions both in respect to their anatomical location and in degree of seriousness to the patient. In addition to the cases recorded in this table we have also recovered anaerobic nonhemolytic streptococci from cultures of the throat, sputum, vagina, urine, and feces. Because these do not represent instances of surgical infections they have not been included in this report.

An analysis of this material reveals that infections associated with the gastrointestinal tract are responsible for 84 or 49.41 per cent, of all cases. As would be expected Escherichia coli is the organism found most frequently in conjunction with the anaerobic nonhemolytic streptococcus in these lesions. In the group of 84 cases there are 28 instances of perirectal abscess. As has been pointed out previously from 9 of these cases streptococci were isolated in pure culture, and in 5 of the 19 remaining the only other organism present was an anaerobic Gram negative bacillus.

Seventeen plueropulmonary infections form another large group. Again as would be expected fusiform bacilli, spirochetes, and vibrios, usually diagnosed by smear, were the most frequently associated organisms.

Of a total of 13 cases of infected pilonidal cysts in which the anaerobic nonhemolytic streptococcus was present 4 yielded this organism in pure culture. In the 9 remaining cases the most frequently associated organism was the nonhemolytic Staphylococcus aureus which was present in 5 cases.

There were 7 infected sebaceous cysts. Three contained the anaerobic nonhemolytic streptococcus in pure culture, in one other it was present with Staphylococcus albus only, and in another the only associated organism was Bacillus subtilis.

A further analysis of the various organisms identified in conjunction with the anaerobic nonhemolytic streptococcus can be made from Table IV.

McDonald, Henthorne, and Thompson recovered anaerobic streptococci from the heart's blood of a fatal case with perirectal abscess, pelvic peritonitis, retroperitoneal and scrotal abscess, following a perforated carcinoma of the rectum.

TABLE IV.—THE INCIDENCE OF THE ORGANISMS RECOVERED IN ASSOCIATION WITH THE ANAEROBIC NONHEMOLYTIC STREPTOCOCCUS—141 CASES

	Cases
Anaerobic Bacteria	
Clostridium welchii	16
Spirochetes	6
Fusiform bacilli	10
Vibriones	5
Actinomyces	3
Bacteroides group	4
Gram positive cocci, unclassified	1
Gram positive bacilli, unclassified	3
Gram negative bacilli, unclassified	15
Microaerophilic bacteria	
Hemolytic streptococcus	9
Aerobic bacteria	
Streptococcus hemolyticus	12
Green streptococcus	34
Staphylococcus albus	7
Staphylococcus aureus nonhemolytic	36
Staphylococcus aureus hemolyticus	29
Micrococci	2
Bacillus subtilis	7
Diphtheroids	8
Escherichia coli	46
Bacillus proteus	10
Aerobacter aerogenes	5
Bacillus fecalis alkaligenes	2
Bacillus pyocyaneus	8
Gram negative bacilli, unclassified	9

Other than this, however, we have not been able to find reports in the literature dealing with the recovery of the nonhemolytic anaerobic streptococcus either alone or in association with other organisms from the pus of perirectal abscess, nor from infected pilonidal cysts or infected sebaceous cysts. These 3 groups of cases in our series are particularly noteworthy in this respect.

EVALUATION OF STUDY

It is apparent from the foregoing review and report of cases that the anaerobic nonhemolytic streptococci, in addition to being normal inhabitants of the oral cavity, gastrointestinal tract, female genitourinary tract, and skin surface, can be isolated from a wide variety of infectious processes in nearly all human tissues. The question as to whether or not anaerobic nonhemolytic streptococci are pathogens and if they are, whether they play etiological rôles in the cases presented is a natural inquiry and a subject with which this

[5]Posttraumatic ulcer; postirritation ulcer; ulcer secondary to burn; chronic nonspecific ulcers (3).
[6]Abscesses of: axilla; neck; superior maxilla; subperiosteum; submaxillary abscess.
[7]Infection of: burn (2); lip; popliteal space; great toe; amputation stump (3); epithelioma of vulva; carcinoma of breast; axillary granuloma; furuncle of face.

study has been concerned. This point has been raised repeatedly and as yet there is no satisfactory answer. That they are residents of certain organs in many instances as harmless saprophytes must be granted. Undoubtedly, in certain instances the pathogenic rôle is assumed only when the tissues of the host have been subject to some alteration, such as trauma, necrosis, diminished blood supply, or chemical changes.

There is an abundance of evidence pointing to the fact that they are definitely pathogens for man, either alone or in symbiosis with other bacteria. This is convincingly demonstrated in puerperal infections when, in some instances, it is possible to recover the organisms in pure culture from thrombosed pelvic veins, the blood stream, and distant metastatic abscesses. In our own group of cases, the chief basis for assuming that these streptococci are pathogens is the finding of them in pure culture in 29 (17.05 per cent), of the cases. This same point is made by McDonald, Henthorne, and Thompson in reference to their series. These authors state that "the frequency with which they [anaerobic streptococci] were found in pure culture lends importance to these organisms as a cause of human inflammatory disease and suggest that they played a significant rôle in all cases in which they were present, whether or not they were the sole pathogens present."

Animal experimentation might throw some light on the subject of pathogenicity. However, in surveying this field we find that the various observers differ in the results which they have obtained relative to the pathogenicity of anaerobic nonhemolytic streptococci for laboratory animals. Lesions have been produced in animals by the use of pure cultures of organisms isolated from human cases. The streptococcus isolated by Veillon produced subcutaneous abscesses when injected into mice and guinea pigs. Marwedel and Wehrsig injected anaerobic streptococci from one of their cases of gas gangrene into a guinea pig and hemorrhagic gangrenous and gaseous edema and death ensued in 12 hours. Anaerobic streptococci were recovered from the diseased tissue. After repeated passages on artificial media this organism lost its virulence and would no longer kill guinea pigs. Mendel was able to reproduce in rabbits lesions resembling pyorrhea by subgingival injections of pure cultures of Streptococcus parvulus. Numerous other instances illustrating the pathogenicity of the anaerobic streptococcus for laboratory animals are recorded. However, the consensus among the writers is that, in general, laboratory animals are refractory to this organism. Our own experience with tests for animal pathogenicity has been limited. Experimentation along these lines should be carried out, particularly with those strains which are the only organisms isolated from a given lesion.

An adequate system for the classification of the anaerobic nonhemolytic streptococci is lacking. It is in this field that a golden opportunity for further work with these organisms is presented. Our experience with Prévot's classification has not been satisfactory. We have attempted to classify 37 of our strains, using as a basis the criteria suggested by him. In 23 instances classification was not possible because of the many incompatibilities with the biological reactions which are supposed to delineate the various type species. The 14 remaining strains were identified as follows: Streptococcus intermedius, 6; Streptococcus micros, 5; Streptococcus anaerobius, 1; Streptococcus putridus, 1; Streptococcus evolutus, 1. Each proposed classification has been based on studies of rather small numbers of strains and as far as the classification of the anaerobic nonhemolytic streptococci are concerned, we are sympathetic with the view of Dack who has stated that the anaerobic nonspore forming organisms, including the streptococci, "have been assigned names and characteristics on the basis of inadequate study."

It is worth repeating that the cases recorded in this report together with the review of the literature serve to emphasize the fact that the anaerobic nonhemolytic streptococci can be isolated from a widespread variety of sources. The importance of this fact should not be minimized, and a search for this organism should be made particularly in those surgical infections which cannot be explained on the basis of the organisms recovered from aerobic

cultures. The value and importance of anaerobic, in addition to aerobic, studies by laboratories concerned with the bacteriological diagnosis of material from surgical infections is evident and can not be overemphasized.

SUMMARY AND CONCLUSIONS

The literature dealing with the anaerobic nonhemolytic streptococcus, its habitat, cultural characteristics, and infections associated with it has been reviewed. We have reported 170 cases of various types of surgical lesions occurring on a general surgical service from which this organism was isolated. Twenty-nine of these cases showed anaerobic nonhemolytic streptococci in pure culture. Recovery of this organism in pure culture, as well as in association with other organisms, from cases of perirectal abscess, infected pilonidal cysts, and infected sebaceous cysts is reported for the first time.

There is as yet no adequate system for the classification of the anaerobic nonhemolytic streptococci.

These organisms form a part of the normal flora of the human mouth, intestine, and female genital tract. They are usually present in the rôle of harmless saprophytes; however, under certain conditions because of alterations either in the bacteria themselves or in the host, or because of symbiosis with other microorganisms present, they are capable of producing inflammatory processes in various body tissues and organs. Among the infections in which this organism plays a part are certain ones of surgical significance. Adequate bacteriological study of all surgical infections should therefore include a search for these organisms and other anaerobes as well as for those of aerobic variety, and this study emphasizes the importance of doing routine anaerobic cultures on all infections.

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THE EFFECT OF THERAPEUTIC DOSES OF X-RAY ON INFECTIONS AND INFLAMMATIONS

Experimental Studies

L. A. WEED, Ph.D., M.D., A. P. ECHTERNACHT, M.D., E. J. MEISTER, M.D., and ROGER ISENHOUR, Indianapolis, Indiana

IN the fall of 1935, two of us (M. and W.) attempted to investigate the manner in which x-rays exert their effect on infectious processes, assuming the validity of the premise that the procedure had merit. Since the results were primarily of a negative nature and the work was unavoidably interrupted, the data were never published. However, in view of military interest in the use of x-ray in the prophylaxis and therapy of wound infection, especially gas gangrene, and since there is no known rational experimental basis to support this method of treatment in Clostridium welchii infection, we have undertaken a reinvestigation to see if we might possibly obtain experimental data to substantiate the growing clinical belief that irradiation is of value in treating human infections. It is the purpose of this paper to present data on the effect of x-rays on infections due to Clostridium welchii, on the organisms and their toxins, and on the toxins of Staphylococcus aureus and Corynebacterium diphtheriae. Part of the data was obtained in the fall and winter of 1935—1936 at the State University of Iowa, the remainder in the summer and fall of 1941 at the Indiana University Medical Center.

Effect of x-rays on Clostridium welchii infection in guinea pigs. Guinea pigs of about 400 gram weight were injected intramuscularly in the thigh with a 24 hour culture of Clostridium welchii. The experiments in 1935 were performed with a culture recently isolated from a case of gas gangrene of the orbit at the General Hospital, State University of Iowa. Preliminary determinations indicated that a 0.10 cubic centimeter dose of a 24 hour chopped meat culture injected intramuscularly into the thigh would kill the animals regularly in 48 hours. This dosage was used to inoculate a series of 12 animals, 6 to be treated with x-ray at varying intervals and 6 to be used as controls. The infected area of each animal was treated 3 times with 100 roentgens, measured in air (1 millimeter aluminum, 140 kilovolts, 5 milliamperes), at 2½, 6½, 11½ hours after inoculation. The experimental and control animals died within 24 hours with no demonstrable effect of x-ray therapy.

We next tried the effect of x-rays on the viability of Clostridium welchii *in vitro*. A 24 hour brain broth culture was filtered to remove the tissue, leaving a uniform suspension of the organisms. The suspension was then divided into five 7 cubic centimeter portions and each was exposed to x-rays in an open Petri dish, respectively as follows: 500, 1000, 1500, and 2000 roentgens (0.3 millimeter aluminum, 133 kilovolts, 5 milliamperes); the fifth sample served as a control. Immediately after treatment the suspensions were plated out to make quantitative counts on the number of viable organisms remaining. No difference could be detected in the 5 samples tested, the number of organisms being the same in each.

We next attempted to determine if x-ray had any effect on the dermonecrotic toxin of Clostridium welchii. The Seitz filtrate of an 18 hour chopped meat culture of the organism was divided into two portions; one untreated, the other treated with 2000 roentgens of x-ray (0.3 millimeter aluminum, 133 kilovolts, 5 milliamperes). The samples were then titrated on guinea pigs for dermonecrotic toxin, the treated filtrate being injected into the skin on the right side of the animal and the same volume of untreated toxin being injected on the left side. The size of the erythema and

From the Departments of Bacteriology and Radiology, Indiana University Medical Center, and the Department of Radiology, University of Colorado School of Medicine, Denver, Colorado.

edema, as well as the elevation of swelling, were carefully measured, but no significant difference could be demonstrated between the reactions to the treated toxin and the control. The hemotoxin (as oxidized lysin) was also measured on the same sample of toxin, by using 1 cubic centimeter of 1 per cent washed sheep cells. Again, no real difference could be shown between the irradiated and the control lysin. All experiments were duplicated to check the possibility of some technical error.

Having failed to demonstrate any real effect of x-ray on infections produced by full grown cultures or on the toxins of Clostridium welchii, we attempted to determine if x-rays could be used to prevent the development of an inflammatory reaction to the toxic filtrate given intracutaneously. Guinea pigs of about 400 gram weight were divided into 2 lots, 1 group treated with 200 roentgens (0.3 millimeter aluminum, 130 kilovolts, 5 milliamperes) 2 hours before inoculation, the other group treated with the same dosage after inoculation. The reacting skin was measured as before, but no difference could be detected between either group and the untreated controls.

In view of the growing interest in military circles, both in the United States and in England, in the use of x-ray as a prophylaxis in Clostridium welchii infection, and because of the continued reports of Kelly claiming value for the method in treating fully developed cases, it was decided to recheck the use of x-ray as a method of treating gas gangrene in the experimental animal. The work was started in August, 1941. We chose as our infecting organism the SR12 strain of Clostridium welchii (type A, Wilsdon's classification) obtained from the National Institute of Health. Preliminary titration showed that 0.10 cubic centimeter of a 24 hour culture was the smallest dose which could be relied upon to kill 50 per cent of guinea pigs weighing 400 grams when injected intramuscularly in the lateral aspect of the thigh. Doses of 0.12 cubic centimeter or more killed the animals in 12 to 20 hours and smaller doses (0.08 c.c.) killed only an occasional animal. We found that animals surviving 3 days without treatment invariably recovered spontaneously. A total of 40 animals inoculated with the standard dose was divided into 4 groups of 10 each to receive respectively 50 roentgens, measured in air (100 kilovolts, 8 milliamperes, no filter) twice daily, 25 roentgens twice daily, 100 roentgens daily, and an untreated control group, the first treatment to start 6 hours after inoculation of the animals. Two animals in the group receiving 100 roentgens daily recovered from the infection; all other animals including the controls died within 30 hours after inoculation. We therefore repeated the experiment using 135 guinea pigs divided into 3 groups of 45 each receiving varying amounts of culture, namely, 0.15, 0.10, and 0.08 cubic centimeter. Graded doses of culture were used to allow for variation in growth and to be reasonably certain of having at least one group of animals surviving long enough to receive two doses of irradiation. Fifteen of each group were treated with 75 roentgens (100 kilovolts, 8 milliamperes, no filter) twice a day, 15 were treated with 100 roentgens once a day, and the remaining 15 served as controls. X-ray therapy was given 3 hours after inoculation. In each of these experiments animals receiving treatment twice daily received the second dose 8 hours following the first. The few which survived long enough to receive the scheduled second daily dose were treated 24 hours after the initial irradiation. Table I shows clearly the ineffectiveness of the treatment.

TABLE I.—EFFECT OF X-RAY THERAPY ON CLOSTRIDIUM WELCHII INFECTION OF GUINEA PIGS. TREATMENT STARTED 3 HOURS AFTER INFECTION

Volume of infecting dose c.c.	Animals	Amount of x-ray therapy	No. of recoveries
0.15	15	Untreated	0
	15	75 r 2 times daily	0
	15	100 r 1 time daily	0
0.10	15	Untreated	0
	15	75 r 2 times daily	0
	15	100 r 1 time daily	0
0.08	15	Untreated	1
	15	75 r 2 times daily	0
	15	100 r 1 time daily	0

Effect of x-rays on toxin production. In order to determine whether x-rays had any effect on toxin production, young (3 hour) brain broth cultures of Clostridium welchii were treated

with 500 roentgens each (0.3 millimeter aluminum, 130 kilovolts, 5 milliamperes) at 3, 5, and 7 hours. The cultures were then centrifuged at high speed to remove the bacterial cells and thus to avoid the removal of the small amount of toxin present by use of a filter. The supernatant fluids were titrated for the dermonecrotic toxin by using guinea pigs as test animals. In three separate experiments no inhibition of toxin production could be demonstrated. Total counts made on the young, actively growing cultures showed no difference in the rates of growth between the control and treated cultures. Repeated tests with up to 5000 roentgens showed no inhibition of growth rates or production of toxin.

Effect of x-ray on diphtheria toxin. Stabilized diphtheria toxin was dispensed in 10 cubic centimeter quantities in Petri dishes and treated with 200, 500, 1,500, and 3,000 roentgens (0.3 millimeter aluminum, 133 kilovolts, 5 milliamperes). Varying dilutions of the toxin samples were made and tested intracutaneously in white rabbits to determine the minimal reacting dose in the skin. No definite effect was demonstrated (Table II).

TABLE II.—EFFECT OF X-RAY ON STABILIZED DIPHTHERIA TOXIN

Volume toxin c.c.	Total volume injected c.c.	Erythema produced after treating toxin with the following doses of x-ray				
		3000 r	1500 r	500 r	200 r	Untreated
0.00006	0.1	15 mm.	15 mm.	15 mm.	15 mm.	15 mm.
0.00003	0.1	15 mm.	15 mm.	15 mm.	15 mm.	15 mm.
0.000015	0.1	12 mm.	12 mm.	8 mm.	12 mm.	12 mm.
0.0000075	0.1	10 mm.	10 mm.	10 mm.	10 mm.	6 mm.

Effect of x-ray on the toxins of Staphylococcus aureus. Powdered Staphylococcus aureus toxin, received from the National Institute of Health was dissolved in saline and diluted for preliminary titrations to determine the minimal hemolytic dose for 1 per cent rabbit erythrocytes and the minimal dermonecrotic dose for guinea pigs. Ten cubic centimeter amounts of the toxin were treated with 200 and 1000 roentgens, respectively (0.3 millimeter aluminum, 133 kilovolts, 5 milliamperes), the control being left untreated. Titrations of hemolysis are shown in Table III.

TABLE III.—EFFECT OF X-RAY ON THE HEMOLYSIN OF STAPHYLOCOCCUS AUREUS

Condition of toxin	Volume of toxin in c.c.					
	0.05	0.025	0.0125	0.00625	0.003125	0.0015625
Untreated	4+	4+	4+	2+	0	0
200 r	4+	4+	4+	2+	0	0
1000 r	4+	4+	4+	2+	0	0

Table IV shows effect on the dermonecrotic toxin.

TABLE IV.—THE EFFECT OF X-RAY ON THE DERMONECROTIC TOXIN OF STAPHYLOCOCCUS AUREUS

Condition of toxin	Volume of toxin injected in total volume of 0.1 c.c.			
	0.001 c.c.	0.005 c.c.	0.0025 c.c.	0.00125 c.c.
Untreated	10 mm. necrosis	4 mm. necrosis	No reaction	No reaction
2000 r	10 mm. necrosis	4 mm. necrosis	No reaction	No reaction

EVALUATION OF STUDY

Clinicians have long been impressed with the therapeutic effects of x-ray in infectious processes in humans. However, the literature is devoid of convincing experimental data, either as controlled human cases or animal inoculations substantiating this point of view. It is quite probable that many investigators have performed experiments attempting to obtain confirmatory information in the experimental animal. The absence of such evidence in the literature leads us to infer that they have failed in their efforts, but hesitated to make a negative report. It is realized that data obtained in animals may not be interpreted to apply directly to humans, especially may this be true in the case of gas gangrene due to Clostridium welchii. Guinea pigs inoculated with Clostridium welchii usually die within 48 hours or recover spontaneously. We have never been able to find a dosage of culture which would consistently kill the animals on the 4th, 5th, or 6th day. Those claiming benefit from x-ray in gas gangrene criticize the use of the guinea pig as the experimental animal because the condition is one of such rapid intoxication. On the other hand they claim dramatic results in certain cases of x-ray therapy in individuals moribund and even

comatose. Certainly these latter cases, would simulate the condition in guinea pigs injected with a minimal fatal dose and treated 3 hours after infection. In clinical work one could hardly hope to have a case earlier than this unless x-ray is used prophylactically in all wounds. Then one is not treating gas gangrene.

Another difference between practical x-ray therapy in humans with gas gangrene and guinea pigs infected with known pure cultures of Clostridium welchii is the etiology of the disease. Most clinicians consider as gas gangrene any condition of injury with local swelling and gas in the tissue as shown by palpation or roentgenograms. Thorough bacteriological examinations are not made in the majority of cases of so called gas gangrene. In those cases examined bacteriologically the customary procedure is to look for gram-positive organisms morphologically similar to Clostridium welchii. It should be emphasized that this does not make a positive bacteriological diagnosis of Clostridium welchii infection, even in the presence of gas in the tissue. It is sufficient to indicate a clinical diagnosis but not for a strict bacteriological diagnosis so one may compare the treated human case with experimental infections in which known organisms are used.

If one were to admit the value of x-ray in the treatment of Clostridium welchii gas gangrene in humans, it would be of interest to know the mechanism by which this is brought about. Since the disease is primarily one of rapid intoxication, one might suspect the effect would be on the toxin. This view is also suggested by certain reports claiming dramatic results in cases in which the patient is *in extremis*. We have been unable to demonstrate any deleterious effect of x-ray, even in large doses, upon Clostridium welchii toxin *in vivo* or *in vitro*. At times we were inclined to believe the treated toxin was more active than the control but the differences were not marked. Certainly there was no evidence the dermonecrotic or hemolytic factors were reduced in the slightest. The effect of huge doses of x-ray was not tried since they were outside the realm of possible therapeutic application. It is interesting that treatment of the local area immediately after injection of the toxin had no effect on the rate of development or degree of tissue reaction to the toxin.

The development of toxin by Clostridium welchii *in vitro* is known to take place in the rapidly growing phase of the growth curve. It is also known that in solution the toxin tends to disappear rapidly. One might consider, therefore, that possibly x-rays would retard the rate of formation of toxin and allow the body to develop active immunity or that it would accelerate the rate of deterioration of toxin. We were unable to show either effect.

SUMMARY AND CONCLUSIONS

1. In guinea pigs x-rays had no beneficial effect in the treatment of gas gangrene due to Clostridium welchii.

2. They were ineffective in reducing the number of viable vegetative forms of a 2 hour culture of Clostridium welchii.

3. They were ineffective in retarding the rate of growth of Clostridium welchii.

4. They did not prevent the development of hemolysin or dermonecrotic toxin of Clostridium welchii.

5. They would not prevent the development of dermonecrosis even if applied before or immediately after the injection of Clostridium welchii toxin.

6. They would not inactivate either the hemolysin or dermonecrotic toxin when applied *in vitro*.

7. They would not inactivate *in vitro* either the hemolysin or dermonecrotic toxin of Staphylococcus aureus.

8. They would not inactivate *in vitro* the toxin of Corynebacterium diphtheriae.

We are well aware of the fact that data obtained by treating Clostridium welchii infections in guinea pigs may not represent the results one would obtain by treating similar conditions in humans. It must not be forgotten, however, that the data presented in this report include not only experiments on infected animals, but also *in vitro* experiments on rates of growth, rates of toxin production, and attempts to destroy toxins *in vivo* and *in vitro*. In no experiment has any real effect been demonstrated with doses of x-ray even beyond that permitted for human therapy.

PRIMARY CLEANSING, COMPRESSION, AND REST TREATMENT OF BURNS

VINTON E. SILER, M.D., Cincinnati, Ohio

THAT burns occur frequently and constitute one of the most serious problems in medical practice is accepted by all of us. The treatment of a burn has varied in many respects from time to time, and a review of the methods (4, 5, 8, 11, 12, 14, 16, 17, 19) cannot be discussed here. In the literature one is impressed by recent added knowledge in handling such cases through the efforts of the surgeons and those of the physiologists.

Burns constitute a degree of injury to the skin and underlying tissue which we recognize as being first, second, or third degree in extent. There is more to the picture than mere cutaneous destruction and the physiological phase must be emphasized. In any burn the vascular bed of the area has been seriously affected. Blalock (3, 7, 18) and other observers have definitely shown that in such an injury there is marked increased capillary permeability bringing about not only loss of blood plasma, of plasma proteins and electrolytes from the burned surface but also into the surrounding tissue. This loss, in turn, causes a diminished blood volume, decreased minute cardiac output, vasoconstriction, circulatory stagnation, tissue anoxia, and, in severe untreated cases, circulatory failure and collapse. If this picture is of sufficient magnitude so called "thermal shock" will follow immediately. It is not improbable that if it were possible to prevent the loss of blood plasma, of plasma proteins and electrolytes by any method, whether by internal or external medications or by mechanical or chemical means, so called "thermal shock" not only could be alleviated but could practically be prevented.

From the Department of Surgery of the College of Medicine of the University of Cincinnati, Cincinnati General Hospital, and the Children's Hospital, Cincinnati, Ohio.

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The injury produced by a burn is an open wound and is comparable to traumatic open wounds. Most burns are contaminated because they are exposed to the air, and to people hovering over them, allowing bacteria from the uncovered nose and throat to fall upon them. Not infrequently they are grossly infected by the application of home remedies. During the past 10 years the surgeons have proved that infected wounds, treated early, can heal primarily if properly cleansed and débrided. In brief, we advocate essentially this: that a wound resulting from a burn can be converted from a potentially infected wound into a surgically clean one by the same surgical principles, enabling healing *per primam* or at least minimizing the infection. Prevention of infection is probably the most important single factor in the treatment of burns. Many observers, particularly Aldrich, have proved beyond question of doubt that so called "toxemia" and the clinical course is not only dependent upon the degree of infection, but also upon the type of organism found in the infected wound.

These relatively recent pathological concepts which have been set forth are responsible for the presentation of a method advocated by Koch, Mason, and Allen (2, 13, 15) and modified by us. It can rightfully be called "Primary Cleansing, Compression, and Rest Treatment of Burns." This procedure is outlined briefly in the following paragraph.

A burned patient is an emergency and must be seen immediately upon entry into the hospital. All nurses and doctors should wear caps and masks when handling such a patient. A rapid general examination will establish the presence of "thermal shock." Pain should be alleviated by the administration of morphine to adults and codeine to children. We believe that surgical cleansing and débridement can best be done only in the operating room and under general anesthesia. Ideally, the patient

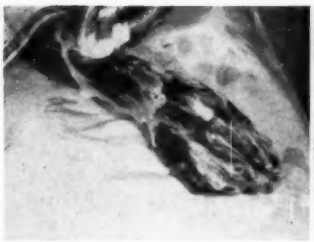

Fig. 1. Washing of the wound with white soap and water for 10 minutes.

Fig. 2. Irrigation of soap from the wound by use of physiological saline solution.

Fig. 3. Removal of blisters and necrotic skin being carried out.

is placed on the table upon a sterile sheet and in position to facilitate best cleansing. General anesthesia is administered. The surgeons having been gowned and gloved in the usual fashion after scrubbing for 10 minutes, drape the involved region with sterile towels and sheets. The wound is gently washed with white soap and water for 10 minutes (Fig. 1). The soap is irrigated from off the area, physiological saline solution being used (Fig. 2). Gross débridement is carried out during this procedure (Fig. 3). The surgical team changes gown and gloves after which the area is redraped. With the use of fresh instruments and containers a more minute débridement is now done, and the wounds are gently washed a second time with white soap and water. Irrigation is carried out by means of physiological saline. The wound is covered with sterile fine mesh, single thickness vaseline gauze strips (Fig. 4) on top of which are placed flat gauze dressings, followed with fluffed sponges. Pressure is exerted with a folded gauze roll (Fig. 5). Firm uniform compression is obtained not only upon the wound itself but also upon the surrounding tissue by applying large sterile sea sponges or sterile "mechanic's cotton waste," held with another folded gauze roll (Fig. 6). The dressing is made a complete surgical one by means of adhesive tape which maintains the pressure and aids immobilization of the involved part. In some instances light plaster casts have been applied. This dressing is allowed to remain untouched for from 8 to 14 days. In the case of first and second degree burns the wounds should be completely healed when the dressings are removed while in the case of third degree burns, the wound usually allows the application of a split thickness graft as advocated by Blair and Brown. If there is mild infection of the granulating wound postage stamp Thiersch grafts may be safely applied. In the rare instances of gross infection the wounds must be prepared for grafting by suitable means.

In a series of more than 100 cases treated at the Cincinnati General Hospital and the Children's Hospital we have proved to ourselves beyond the question of a doubt that one can convert a potentially infected burned wound into a surgically clean one.

We have good reasons to believe that surgical compression dressings will prevent so called "thermal shock." It should be clear in the minds of all that since severely burned patients lose large amounts of blood plasma, hemoconcentration occurs. Concomitantly, the loss of plasma proteins and electrolytes aids in mobilization of the blood plasma at the site of injury as is shown by the edema at that point. Therefore, whole blood transfusion or administration of parenteral fluids is contraindicated since the former gives rise to further hemoconcentration and the latter increases local edema, which means loss of more plasma, plasma proteins, and electrolytes. Blood plasma should be administered to control this abnormal physiology. Our clinical research reveals that surgical compression dressings aid materially in preventing this pathologic-physiological syndrome. Splinting of involved extremities in the position of function either by sterile aluminum splints or plaster casts aids greatly in wound healing and also in prevention of not infrequent serious contractures.

Fig. 4. Covering of the cleansed wound with sterile fine mesh, single thickness vaseline gauze strips.

Fig. 5. Formation of a pressure dressing by use of a folded gauze roll.

Fig. 6. Uniform pressure being exerted on wound and surrounding tissue by "sterile mechanic's waste."

Plastic repair must not be minimized and wounds larger than a quarter in size should be grafted as soon as possible. The application of split thickness grafts or of small postage stamp Thiersch grafts is a matter of personal opinion. Skin replacement is the important feature.

As soon as the surgical compression dressing has been applied and the patient is in his bed, his general condition becomes the concern of those attending him.

Other than the clinical and laboratory observations made, there is little else to do except see that nursing care is adequate. Certainly the one great advantage this method has over other forms of treatment is the fact that no further local treatment is necessary. We have insisted on charting temperature, pulse, and respirations every half hour for the first four postanesthetic hours and every 4 hours thereafter. During the first 24 hour postoperative period the blood pressure should be observed frequently. It is important that the fluid intake and output of these patients be recorded in daily periods. A daily urine analysis should be reported until the patient is past the danger zone. It is important that the amount of fluid intake is within reasonable limits. Where one has facilities for capillary hematocrit (10), specific gravity and plasma protein determination (9), the control of fluid therapy should be much more accurate than by mere clinical impressions. Also, the indications for whole blood or blood plasma transfusion are shown by these observations. Using "Primary Cleansing, Compression, and Rest Treatment" we have found, particularly in the case of children, as well as in adults, that these patients rapidly assume their own water balance by oral fluid intake and that parenteral administration is required only in the more severe cases. These patients are given high protein diets as soon as possible, and it has been our experience that solid food is fully enjoyed by the second or third day in most cases.

Morphine sedation should be used when pain is intense; however, as soon as possible codeine should be substituted. We believe that the use of codeine in the case of children is much safer than morphine.

In keeping with recent advances of vitamin therapy in wound healing and also in infection, we have given a vitamin B complex with ascorbic acid in capsule form. At this time we are unable to draw any conclusions as to whether or not this medication is beneficial in burned patients.

From a purely scientific standpoint it is desirable to have daily white and red blood cell counts, hemoglobin, plasma protein blood chloride, nonprotein nitrogen or urea nitrogen determinations, and a carbon dioxide content of plasma. If one suspects liver damage in the case of severe burns, an icteric index and blood cholesterol should be obtained.

From a practical standpoint, such examinations would not only be expensive, but are not always available. Much can be learned from examination of a daily urine, red and white blood cell counts, a hemoglobin determination, and the clinical course of the patient.

Another advantage that this method has over other forms of treatment, particularly the tannic acid silver nitrate method, is that after the initial dressing these patients are easily able to move or be moved in bed. This certainly inhibits the onset of upper respiratory tract infection and pneumonitis which sometimes become serious complications. In the case of children we have been impressed by the fact that they not only frequently stand up in their cribs by the third or fourth day but that they play with their toys and seem to enjoy themselves. They have displayed more contentment with compression dressings than those cases treated otherwise. These facts have not only been observed by the attending doctors but also have vividly impressed the nurses in charge of them.

CONCLUSIONS

1. A method of treating burns has been advocated which will reverse the pathologic-physiology presented by such cases.

2. This method advocated by Koch and Mason and modified by us, we believe, has definite advantages as compared with other methods of treatment.

Briefly enumerated, these are: (a) Infection is entirely prevented or minimized and this fact abolishes the toxemia and the febrile clinical course usually seen. (b) With sterile compression dressings it is believed that "thermal shock" and the complex blood concentration syndrome are prevented. (c) With the immobilized surgical compression dressing the involved area heals *per primam* in the case of first and second degree burns, In the case of third degree burns, the granulating tissues by virtue of their cleanliness allow for plastic repair much sooner than any other known method of treatment. In any case, hospitalization is shortened. (d) There are certain definite advantages from a nursing standpoint in the use of this form of treatment. Some of these are: ease in handling the patient, general well-being of the patient, unrestrained activity which prevents complications such as pneumonia, a definite saving of dressings and hospital linens, and probably one of the most desirable features is the fact that children who are burned do not suffer psychotic changes which usually come from long periods of multiple daily moist dressings.

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THE EXCLUSIVE USE OF SOAP AND WATER IN TRAUMATIC WOUNDS

ROBERT LEE KERRIGAN, M.D., F.A.C.S, Michigan City, Indiana

IN an endeavor to approach the results of Koch and Mason (7, 9) in the treatment of complicated compound wounds, we adopted their method 5 years ago for the manifold occasions presented by the accidents occurring in large industries. The method, while stressing meticulous primary wound cleansing with soap and water followed by excision of only devitalized tissue, does not predicate a sacrifice of, or lessening of emphasis on, any of the other particulars of treatment. Because of its simplicity and universal applicability, no attempt was made to alter any element of therapy; even though during this period the local use of sulfonamides, the newer detergents, and nonirritating metals have had a profound influence in determining some contemporary procedures.

Although it is apparent from a review of recent works that there are still many differences of opinion in regard to treatment, it is to be noted that during the past 5 years the use of the commoner antiseptics in a wound is more generally discouraged (1–7). It is chiefly with respect to the methods of débridement, chemotherapy, primary plating, and closure that the major differences exist; but it is also clear that the problem of the surgical cleansing of a wound is by no means agreed upon.

It is in relation to the latter aspect of therapy that the present study was made. It has been the experience of every surgeon to observe the occurrence of localized infection, tetanus, or septicemia following minor compound contusions, lacerations, and burns when the primary care has been of an accepted standard.

The increasing weight of evidence brought forth in comprehensive surveys of infection rates in excellent hospitals has made it apparent that there has been something quite inadequate even in the preparation of cases for elective surgery. Of all the factors having to do with treatment of damaged and contaminated tissues, the one most likely to be variable and most subject to oversight is that of painstaking cleanliness of the wound itself. It is then of all times that patience and thoroughness are most vitally necessary. There does not exist after the first few hours another opportunity for the accomplishment of the cleansing which should be done at the earliest practicable moment.

This need not be an onerous duty or surgical drudgery. The time devoted to wound cleansing may also be given over to a more accurate appraisal of the anatomical and pathologicophysiological problems at hand, to a formulation of an orderly rather than a hastily planned mode of procedure, and may give the assistants and nurses a valuable opportunity to have available for the surgeon any unusual or additional instruments or materials necessary to meet the situation.

The time required for proper attention to soap and water application will necessarily depend chiefly upon the kind and degree of contamination and the size of the wound, but it is difficult to conceive of a workmanlike preparation of the intact skin in less than 10 minutes and a similar or much longer period for care of the depths of the wound. There is one certainty: the more assiduous the primary cleansing the less likelihood will there be of infection and frequent subsequent dressings. The total time devoted to any individual case is much more likely to be greatly reduced and with infinitely greater safety. Also the time taken to cultivate patience, thoroughness, and judgment in one's surgical group, including internes and nurses, will be many times repaid.

As a matter of necessity, industrial nurses and surgical assistants will assume by far the major portion of the care of the lesser industrial wounds. In no instance, however, is the care of the skin of a complicated wound, that

is, one involving exposed or injured tendons, nerves or bone, delegated to orderlies or nurses. This work should be done by or under the direct supervision of the surgeon in charge.

Since the early days of antiseptic surgery, the use of tincture of green soap has been advocated for the cleansing of surgical wounds of all nature. In the exhaustive bibliography which the subject of wound treatment entails, the washing of wounds has been overshadowed in importance by the emphasis placed upon antiseptic agents or some particular phase of treatment. From the time of Lister to World War I, few stressed as urgently as Davison an exacting mechanical cleansing of the skin and the avoidance of the use of potential chemical irritants in the wound or on the surrounding surfaces. After the war, the general acceptance of Dakin's solution as such, or in modified form, and the newer germicidal solutions that appeared at short intervals did much to obscure the value of, and delay the institution of, rigid cleanly methods. The method we adopted has proved to be as nearly painless as any surgical treatment can be, and the results have been such as to give us every encouragement to perfect ourselves in the details of this mode of treatment.

Alkaline soaps were formerly preferred because they more completely emulsified fat, but prolonged and frequent use is quite irritating to the skin. In the first year of our present work, we used tincture of green soap and in the last 4 years we have used a neutral white soap solution. It is hardly necessary to add that a method which works so well for contaminated wounds may be applied as well to general surgery and most particularly to elective bone and plastic surgery for which aseptic technique must be of the highest order and in which iodine and other common skin antiseptics may be of positive harm. The danger of chemicals causing blistering of skin grafts has been called to our attention by the plastic surgeons. The latter group, too, has done much to show how without aid of chemicals the potentially dangerous regions of the nose and mouth could be made ready for delicate surgical operations by simple cleanly methods.

MANNER OF PREPARATION

The gentle treatment of tissues with a neutral white soap solution applied with sterile cotton balls or gauze constitutes the basic procedure. The wounds, no matter of what nature, are first covered by sterile gauze or packed gently with it while the cleansing of the surrounding skin is in progress. On occasion benzene, ether, or prepared soaps which dissolve oils and greases more rapidly are used on the uninjured skin, but the final cleansing is given with white soap solution to secure a field of neutral reaction and to prevent the feeling of stiffness and dryness that remains after the above agents alone are used. While these substances are not altogether desirable, they probably do little harm to intact skin and are frequently timesaving when the wounds are multiple and the patient is under anesthesia. When there are many wounds in a single individual to be cared for, it is most desirable to have a separate team with a second nurse with her own table, cleansing materials, drapes, and instruments.

When it is felt reasonably certain that the injured area will not be contaminated from the surrounding tissues, attention is given to the wound itself. With a wound of major significance, the care of the intact skin is delegated to a gloved and gowned assistant, while the surgeon in charge is preparing himself for the care of the wound proper. After the draping is completed, the surgeon proceeds with the task of removing loose clots, foreign bodies and devitalized tissues, with a set of instruments prepared especially for this purpose. Particulate material ground into bone surfaces is removed by patient scraping with curette, chisel, or periosteotome. The wound is then cared for in thoroughgoing fashion with soap and water followed by irrigation with normal saline in abundant quantities, used preferably with a catheter so that every recess in the depths may be reached. Inasmuch as is possible, it is during this time that a contaminated wound is made into a fresh, clean, surgical wound.

Reid and Carter have noted that if washing of the wound is carried out before débridement, foreign bodies may be obscured and will, when a tourniquet is used, make it more dif-

ficult to differentiate between living, healthy, and devitalized tissue.

The wound is gently repacked and while the drapes are being removed every attempt is made to make the surrounding area, as well as the table underneath, as dry as possible, so that there will be no contamination through capillarity when the draping for the definitive procedures is placed. The final toweling is done by the assistant who has in the meantime been preparing himself, thus giving the surgeon an opportunity to change his gown and gloves for the consummation of the surgical problem at hand.

OBSERVATIONS FROM STUDY

The present report is concerned with one aspect of the primary care of open wounds, that of cleansing. A program of soap and water washing of wounds to the exclusion of all chemotherapeutic agents has been consistently carried out in 12,044 open wounds over a period of 5 years. Early and repeated rewards in difficult emergencies have given us every encouragement to continue with the adopted procedure. It may be suggested that the establishment of this method of gentle cleansing, as the basic procedure in the traumatic wounds of both industrial and civil practice, be likewise encouraged.

It is to be noted in current reports emanating from the battle-fronts, that there are references to thorough cleansing followed by excision of devitalized tissue and the use of sulfonamides as a primary measure. The many enthusiastic reports of successful results following the primary use of sulfonamides may lead to the neglect of surgical asepsis as did the chemical antiseptics of an earlier day. It is quite possible that the use of the sulfonamide drugs as an adjuvant to well grounded methods of surgical cleansing may be attended by still better results. The evidence to date, however, does not suggest that there can be any relaxation in the exacting practices of surgical techniques.

This survey is likewise concerned solely with the problem of industry but it may confidently be stated that the results in civil surgery are comparable. Porter has made mention of the fact that possibly little danger of tetanus attends the compound injuries of industry. He and others have considered that it was seldom necessary to resort to the use of prophylactic doses of antitetanus serum. A personal experience with 2 cases of fatal tetanus indicates that there is an ever present danger. The first case was a compound fracture of the fifth metatarsal in which tetanus antitoxin was administered upon entry. Tetanus developed some weeks later when the wound had almost healed. The second case resulted from a slight laceration of the tip of the thumb caused by a falling window. These 2 patients were cared for by the iodine and alcohol method. In over 25,000 compound injuries, no gas gangrene has been encountered after any of the crushing wounds.

TABLE I

Year	Total injuries	Total compound injuries	Compound hand injuries	Hospitalized hand infections	Infected compound injuries hospitalized other than hand
1937	5,009	2,550	2,243	4	3
1938	2,345	1,487	1,192	1	1
1939	3,151	1,957	1,498	0	3
1940	4,407	2,257	1,562	2	0
1941	6,450	3,793	2,700	3	1
	21,362	12,044	9,195	10	8

A large percentage of men in industry harbor pathogenic bacteria in the skin, upon entry. It is an everyday experience to see a furunculosis, contact dermatitis, pustular acnes, and particularly minute infected burns complicating fresh wounds. Many injuries were on hands, showing evidence of contamination or infection of previous untreated abrasions, punctures, or burns. The exclusion of these infected areas and the proper cleansing of a compound wound in the neighborhood are almost uniformly successful when patient cleansing meets the demands of the situation.

Because hand injuries have formed such a high percentage of the total injuries studied, and because the hands are so constantly soiled, and so difficult to clean and to keep clean, they perhaps form the most excellent measure of the efficacy of this method.

It is to be noted from Table II, that in every case of hand infection, one or more days had

TABLE II.—SUMMARY OF CASES[1]

Diagnosis	Interval between injury and treatment Days	Number of days hospitalized	Treatment	Comments
1937				
Cellulitis dorsum of foot	21	6	Massive warm wet dressings	Cause undertermined No permanent impairment
Third degree burn of foot	0	19	Massive warm wet dressings	No permanent impairment
Compound fracture both bones of leg	0	73	Primary suture after reduction	Infection which did not delay union
Tenosynovitis index flexors	Several	1	Incision on ulnar side	No permanent impairment
Tenosynovitis thumb flexors	7	2	Incision	No permanent impairment
Tenosynovitis middle finger	14	5	Incision	No permanent impairment
Infected blister thumb	1	1	Incision	No permanent impairment
1938				
Streptococcus cellulitis palm	1	5	Massive warm wet dressings	Hot metal penetration No permanent impairment
Erysipelas following burn	3	10	Serum and sulfanilamide	No permanent impairment
1939				
Burn perineum buttocks and thigh	0	34	Tannic acid	Healed without grafting
Compound comminuted fractures 4th and 5th toes	0	7	Massive warm wet dressings	No permanent impairment
Infected ulnar bursa	5	2	Incision	Puncture wound No permanent impairment
1940				
Infected callus with abscess formation index finger	7	1	Incision and drainage	No permanent impairment
Tenosynovitis flexor tendon index finger	2	13	Incision and drainage	30 per cent permanent impairment
1941				
Puncture wound little finger	1	9	Incision and drainage	No permanent impairment
Infected dorsum of hand	1	1	Massive warm wet dressings	No permanent impairment
Cellulitis of leg	0	10	Massive warm wet dressings	No permanent impairment
Infected dorsum left hand	8	4	Massive warm wet dressings	No permanent impairment

[1]Table shows (1) types of wounds hospitalized, (2) time elapsed between injury and treatment, and (3) type of treatment used.

elapsed before the patient appeared for treatment and, conversely, in 9,195 compound hand injuries, there was not a single instance of hand infection requiring hospitalization when the present cleansing method was instituted within a few hours after injury. It can likewise be seen from the table, that in no instance was there a septicemia and but one prolonged local infection.

In any case that threatened to be of any severity the patient was immediately hospitalized and studied. Aside from the safeguarding of the patient's health, the cost of compensation and loss of time, both to the injured and employer, made it expedient to hospitalize any infection of any severity. This is not to say that we do not encounter more frequent infections. We do. We have many minor infections and wound contaminations with the men continuing at their work if the part lends itself to splinting with a degree of comfort permitting work. These patients are

watched particularly for any tendency on the part of the infection to spread.

While only 2 patients with burns were hospitalized, the burns were the greatest source of these minor infections and contaminations. In the light of the conception of a burn as a contaminated compound wound (11),we feel confident that our failures have been due to insufficient cleansing because of pain elicited, inadequate pressure dressings and to the placing of too much dependence upon tanning agents. We now employ as diligent cleansing methods as in other compound wounds by making the process as painless as possible with local or general anesthesia.

Compound fractures were encountered in 101 patients with 112 fractures with an infection incidence of 4. The majority of these fractures involved the extremities but all parts of the skeleton were affected. There were no cases of osteomyelitis in this series and no cases of delayed union from infection. There was only 1 infection of any magnitude; this occurred in the soft tissues of a both-bone fracture of the leg, but the wound was well healed before the 10th week and the patient walking by the 12th week. These patients were all cared for by doctors in the manner already referred to, and tetanus antitoxin was administered routinely.

There were 445 puncture wounds that received no treatment other than that of a thorough cleansing and débridement at the point of entry and immobilization. No puncture wounds so treated within the first few hours had any subsequent need for hospitalization.

CONCLUSIONS

The study of 21,862 injuries resulting in 12,044 compound wounds, revealed that hospitalization was necessary in 18 cases in which the primary care consisted of white soap and water cleansing and excision of only devitalized tissue. Seventy-five per cent of these compound injuries involved the wrist and hand. Of these 9,195 cases only 10 patients required hospitalization. Because these injuries were so uniformly contaminated and so difficult of cleansing, and further, because in no instance in which primary soap and water cleansing was given, was it necessary to hospitalize an individual for infection, we feel that this is the severest test for the efficacy of the method. It is likewise seen that it is successful in the hands of the nurses who care for the great majority of the minor compound wounds. In 101 cases of compound fractures, there were 4 infections and in no instance osteomyelitis or delayed union from infection.

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THE EXPERIMENTAL PRODUCTION OF GASTRIC AND DUODENAL ULCERS IN LABORATORY ANIMALS BY THE INTRAMUSCULAR INJECTION OF HISTAMINE IN BEESWAX

LYLE J. HAY, M.D., RICHARD L. VARCO, M.D., CHARLES F. CODE, M.D., and OWEN H. WANGENSTEEN, M.D., F.A.C.S., Minneapolis, Minnesota

THE importance of the digestive action of hydrochloric acid of the gastric juice, in the development of ulcer, received a forceful impetus from the experimental production of ulcer in the dog, by the diversion of the alkaline bile and pancreatic juice in the Mann-Williamson operation. The obvious distortion of the normal digestive process, by such an operative procedure, has sufficed to detract from the full significance of the acid factor in the genesis of ulcer. The transplantation of the duodenal segment, into which bile and pancreatic juice are dumped into the reaches of the lower ileum, creates manifestly the potential for a serious nutritional upset. Yet, Matthews and Dragstedt were able to produce ulcers by attaching a closed fundic pouch to sidetracked ileal loops. Whereas Dragstedt feels disposed to ascribe the origin of ulcer entirely to the acid factor, the large number of investigators who have wrestled with the problem of ulcer, including Mann, Ivy, and Ochsner and their associates, incline to the belief that trauma and the nervous factor play important rôles as well.

This investigation was undertaken to appraise the importance of acid gastric juice as produced by histamine stimulation, in the formation of ulcers in the stomach and duodenum.

From the Departments of Surgery and Physiology of the University of Minnesota, Minneapolis, Minnesota.
Dr. Code now at the Mayo Clinic, Rochester, Minnesota.
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About 2 years ago, typical duodenal and gastric ulcers were produced in cats and dogs by the intramuscular injection of a histamine-beeswax mixture. That initial experience was reported briefly (22). It is the purpose of this communication to elaborate upon that preliminary account and to indicate that with employment of this simple instrument, viz., stimulation of the endogenous mechanism for the secretion of acid, duodenal and gastric ulcer may be produced quite regularly in a large number of laboratory and domestic animals.

METHOD

In this study, prolonged histamine action was obtained by embedding histamine in a beeswax mineral oil mixture. This mixture, which melts at temperatures ranging from 40 to 50 degrees C. remains a semisolid mass when injected in the tissues and thus permits a slow and gradual liberation of the embedded histamine. A prolonged, continuous plateau of histamine action is obtained. This method was devised for the study of chronic histamine action (Code and Varco, 1940).

The histamine-beeswax mixture. The histamine-beeswax mixture was prepared in batches using, as a routine, 600 milligrams of histamine dihydrochloride (Hoffmann-LaRoche). The histamine must be dry before it is placed in the beeswax and, since the dihydrochloride is somewhat hydroscopic, precautions should be taken to keep it moisture free. As a rule, sufficient protection from atmospheric water is afforded by keeping the histamine over sulfuric acid in an ordinary desiccator. The histamine is ground to a fine powder in an agate mortar. The grinding is persisted with until

TABLE I.—PRODUCTION OF ULCER IN DOGS WITH HISTAMINE-BEESWAX MIXTURE

Dog No.	Weight pounds	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	35	30	34	Large duodenal ulcer in 1st part of duodenum	No symptoms except tarry stool day before sacrifice
2	27	30	4	Large gastric ulcer on lesser curvature in antrum	Sacrificed when moribund from hemorrhage
3	38	30	21	Four ulcers in duodenum	Dog died of peritonitis from perforation of an ulcer
4	40	30	17	Superficial erosion in duodenum. Two small ulcers on lesser curvature near cardia	Dog sacrificed after having hematemesis
5	22	30	31	Small ulcer in antrum	Sacrificed. Dog had an erosive gastritis
6	17½	30	31	Duodenal ulcer	Sacrificed
7	24	30	12	Two small ulcers in 1st part of duodenum	Sacrificed
8	35½	30	37	Healing ulcer in 1st part of duodenum	Preparation given this dog for 8 days prior to sacrifice was less active than otherwise used
9	27	30	37	No ulcers	Same as Dog 8. Mammillations and few punctate erosions in antrum
10	27	30	7	Five duodenal ulcers, 2 perforated	Expired peritonitis. Was pregnant
11	33	30	23	Three duodenal ulcers, 1 perforated on pancreas	Sacrificed because of distemper with bilateral pneumonia, pregnant
12	34	30	28	Perforated duodenal ulcer	Expired peritonitis. Was pregnant
13	21	30	30	Four superficial ulcers on lesser curvature near cardia	Sacrificed. Dog had had left gastric and right and left gastroepiploic arteries ligated

a smooth homogenous powder is obtained. The powder is removed from the mortar and 600 milligrams exactly weighed. The agate mortar and pestle are heated in boiling water, removed, and dried. The weighed histamine powder is placed in the hot mortar and 0.8 cubic centimeter of melted beeswax is added. These are mixed until homogenous, when 2.8 cubic centimeters of hot mineral oil is added. The contents of the mortar are again mixed until homogenous. While still melted this histamine-beeswax-mineral oil mixture is drawn into 1 cubic centimeter tuberculin syringes which have been warmed and lubricated by rinsing in hot mineral oil. Upon cooling to room temperature, the mixture forms a semi-solid mass which, as a routine, was injected through 20 gauge needles. All doses of hista-

TABLE II.—PRODUCTION OF ULCER IN GUINEA PIGS WITH HISTAMINE-BEESWAX MIXTURE

Guinea Pig No.	Size	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	Adult	5	3	Perforated duodenal ulcer	Expired, peritonitis
2	Adult	5	11	Perforated gastric ulcer. Duodenal ulcer	Expired, peritonitis
3	Adult	5	8	1 pyloric, 3 duodenal ulcers	Expired, peritonitis. One duodenal ulcer perforated
4	Adult	5	7	Gastric ulcer on lesser curvature	Expired
5	Adult	5	2	3 duodenal ulcers	Expired few minutes after histamine injection, perforated ulcer with peritonitis
6	Adult	5	6	3 duodenal ulcers	Expired, peritonitis from perforated ulcer
7	Adult	5	2	No duodenal ulcers	Expired, marked postmortem autolysis of stomach
8	Adult	5	5	No ulcers	Expired, guinea pig was killed accidentally
9	Adult	Mineral oil and beeswax in equal amounts	15	No ulcers	Sacrificed
10	Adult	Mineral oil and beeswax in equal amounts	15	No ulcers	Sacrificed

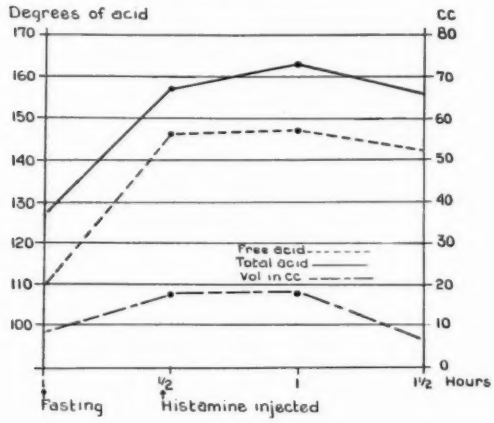

Fig. 1a.

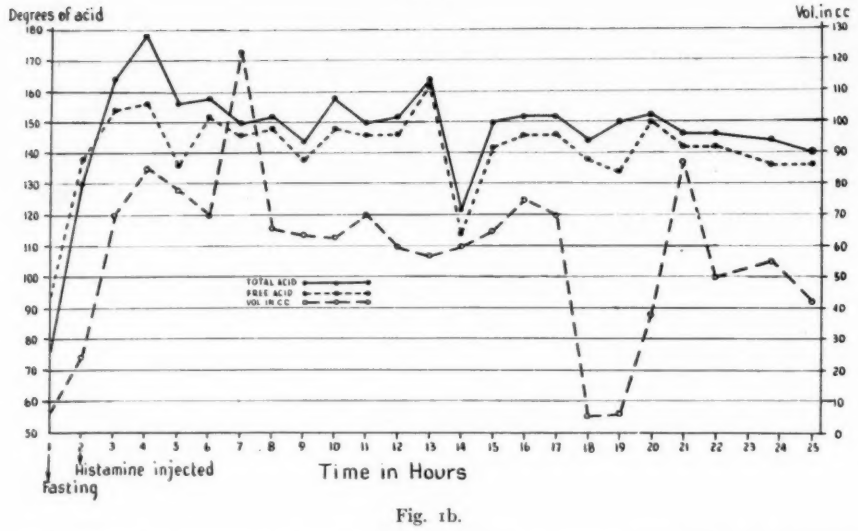

Fig. 1b.

Fig. 1. Graphs of secretory responses to histamine stimulation in dogs with gastric pouches. a, Attending subcutaneous injection of 1 milligram of aqueous solution of histamine. b, Attending intramuscular injection of 30 milligrams of histamine in beeswax. The plateau effect upon the secretion of hydrochloric acid is apparent. Over a period of 24 hours, 1369 cubic centimeters of gastric juice with an average free acidity of 139 degrees was produced. This compares favorably to the response to 1 milligram of histamine, where 36 cubic centimeters of gastric juice with a free acidity of 151 degrees was produced. It will be noted that the volume of juice produced after injection of aqueous solution of histamine had returned to the fasting level after 1½ hours.

mine mentioned throughout this report are in terms of histamine base. The mixture as prescribed gives approximately 100 milligrams of histamine per cubic centimeter.

As a routine, the histamine beeswax mixture was injected once daily in the evening, into the muscles of the back, so that the material was deposited in several pockets along the needle tract. The prolonged histamine action of each batch of mixture was checked by observing the secretion from a Pavlov or Heidenhain gastric pouch after injection of a sample.

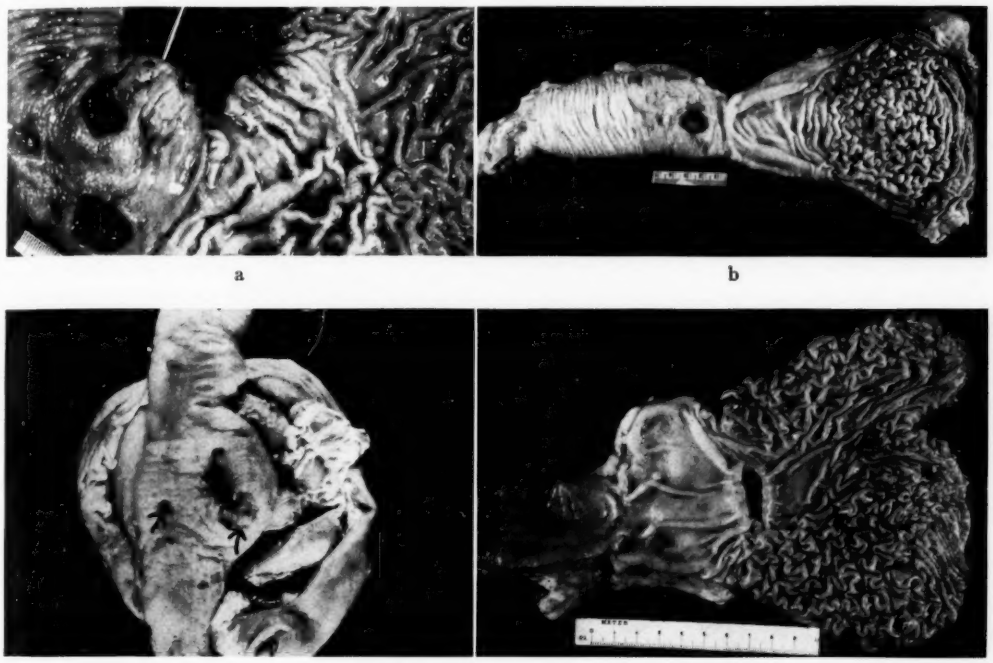

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Fig. 2. Ulcers produced in dogs by the intramuscular injection of a histamine-beeswax mixture. a, Duodenal ulcers with large craters produced in 6 days by the daily injection of 30 milligrams of histamine. b, Typical chronic duodenal ulcer with deep excavation produced after 30 daily injections of histamine base. c, Perforating jejunal ulcer and gastrojejunal ulcer in immediate juxtaposition to the stoma (12). These ulcers were produced in a dog with a gastrojejunostomy after 13 daily injections of histamine base. d, Large bleeding gastric ulcer (Dog 2, Table I) at juncture of mucosa of antrum and corpus. This ulcer occurred after 4 daily injections of histamine base.

Histamine dosage. Adult dogs were given 30 milligrams of histamine base daily in a single injection. This dose was the one found to result in a continuous output of acid from Heidenhain pouch dogs, lasting for 24 hours (Table I). The guinea pigs received 5 milligrams of histamine base daily (Table II). The cats were given from 5 milligrams every 2 days to 15 milligrams of histamine base every day (Table III). The chickens were given 7.5 milligrams of histamine base daily (Table IV). The ducks received 20 milligrams of histamine base daily (Table V); the swine 40 milligrams daily (Table VI). The calves were given from 30 to 150 milligrams of histamine base daily (Table VIII); the monkeys from 20 to 50 milligrams daily (Table IX).

Reactions to the histamine-beeswax mixture. As a rule in the normal intact animals, little or no effects were seen on the injection of a single dose of the histamine-beeswax mixture. In the test dogs, provided with Pavlov or Heidenhain pouches of the stomach, apart from the copious flow of gastric juice from the pouch, the animals appeared normal when given an injection of a properly prepared histamine beeswax mixture. Throughout this study only 4 severe histamine reactions were observed. Two guinea pigs died of respiratory arrest when injected with a mixture made from histamine powder which had taken up atmospheric water and as a result was apparently imperfectly covered by the beeswax. A dog with a gastric pouch, injected with a sample of the same batch of mixture exhibited vomiting and restlessness. The gastric pouch was tardy in responding to the histamine stimulus, owing, it was believed, to the shock associated

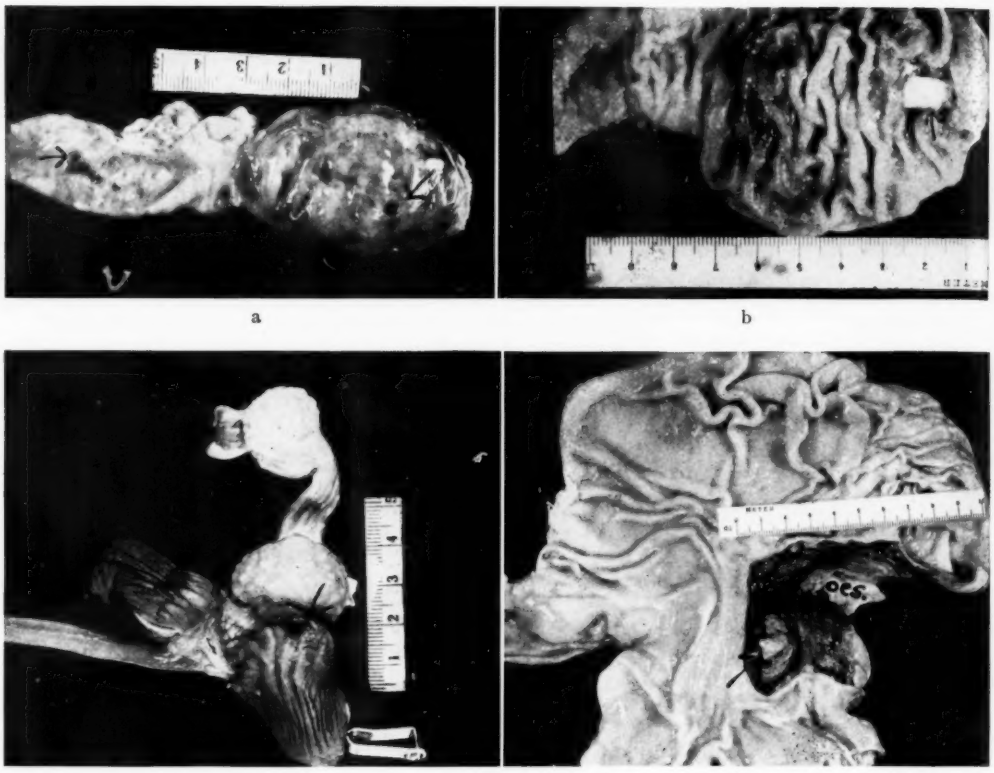

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Fig. 3. Ulcers produced in guinea pig, cat, chicken, and pig by the intramuscular injection of histamine in beeswax. a, Perforated gastric ulcer in the guinea pig; also one large ulcer in the duodenum. Erosions are present in the stomach and duodenum (Table III, No. 2). b, Large perforated gastric ulcer in the cat. The gauze lies on the serous side of the stomach (Table III, No. 1). c, Ulcer in the gizzard of the chicken (Table IV, No. 1). d, Large excavating ulcer present at the cardiac end of the stomach in a pig (Table VI, No. 2). *Oes.* Marks the termination of the esophagus. The arrow points to the pancreas at the site of the perforation.

with the reaction. After an hour the animal had recovered and the pouch secreted at the usual rate. A 3 day old calf developed an asthma-like reaction after the injection of 100 milligrams of the histamine-beeswax mixture and died about 12 hours later of pulmonary edema.

When repeated daily injections of the mixture were given some signs of alterations in the gastrointestinal tract often developed. Toward the end of the injection period anorexia and general apathy were not uncommon. In the dog the occasional passage of a tarry stool was seen and on one occasion hematemesis occurred. Increasing experience taught us that, when the animals became ill, it was likely that an ulcer was present. The experiment was terminated at this juncture by intravenous injection of ether or nembutal. Some of the animals died during the night, of perforation.

Ascertainment of capaciy of stomachs to secrete free hydrochloric acid. In this investigation, it was important to determine whether or not histamine evoked an acid gastric secretion in the different animals studied. Examination for the presence of hydrochloric acid in aspirated gastric juice or vomitus was made in most of the animals. Occasionally determinations of free hydrochloric acid were not made until necropsy. Free hydrochloric acid

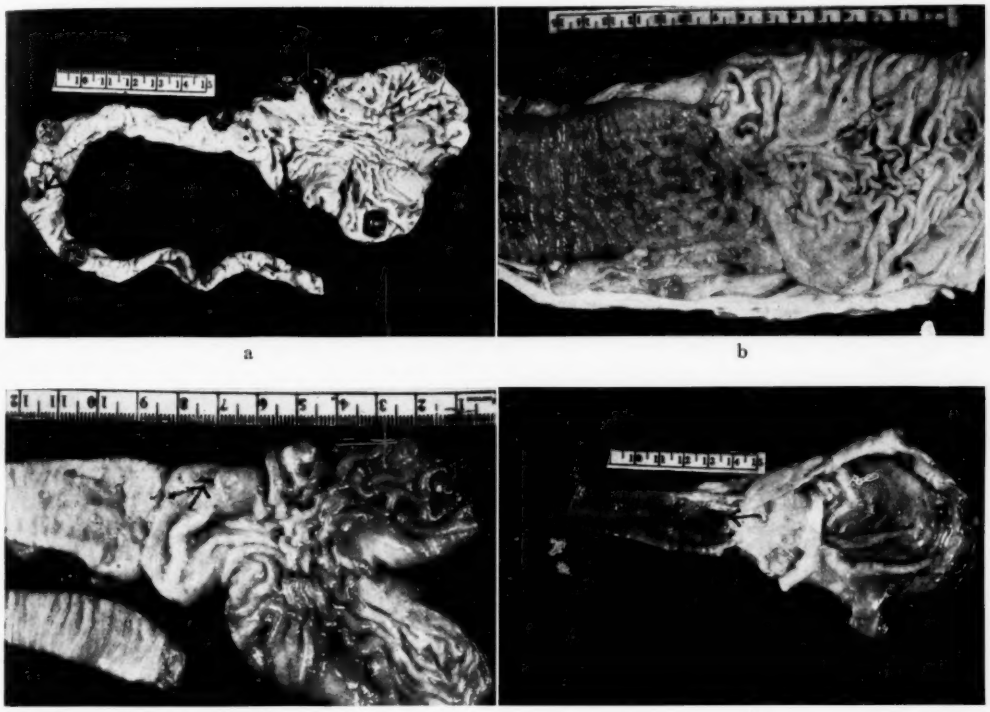

Fig. 4. Histamine ulcers in the woodchuck, calf, monkey, and rabbit. a, The arrow points to a perforation quite low in the duodenum (Table VII, No. 2). There are a large number of gastric erosions. b, Two small ulcers (at arrows) in the calf (Table VIII, No. 6). There are numerous erosions in the stomach and the duodenum. c, The arrow points to a prepyloric ulcer in a monkey. d, Large perforated duodenal ulcer in the rabbit. During the histamine injection period, the rabbit was fed the pressed juice from cabbage, carrots, and lettuce (Table X, No. 4).

was found in the gastric juice of every species of animal studied. It was concluded that histamine stimulated the production of an acid gastric juice in these animals. The free hydrochloric acid in the gastric juice was determined with Toepfer's reagent and the total hydrochloric acid with phenolphthalein, using a tenth normal sodium hydroxide for titration.

Diet of animals during injection period. The diet fed the animals during the period of histamine injection was the same given other animals of the species in our laboratory. The feedings were given in the morning. In the dogs and cats, the food pans were removed from the cages when the injections were made in the evening. In all of the other animals, the food remaining in the cages was left in place. All of the animals were allowed free access to water. The dogs and swine were fed table scraps, supplemented with "Champion" puppy biscuit in the former, and with corn and milk in the latter. The cats received milk and raw hamburger. The guinea pigs, rabbits, and woodchucks were fed oats, fresh carrots, rutabagas, and small animal food pellets. The chickens and ducks were given corn, oats, and milk. The monkeys ate peanuts, bananas, and carrots. The veterinary department at the University Farm cared for the calves. They were fed raw milk, supplemented with hay.[1]

RESULTS

Response from gastric pouches upon injection of histamine-beeswax mixture. Subcutaneous

[1]The authors acknowledge gratefully the helpful co-operation of Dr. Willard L. Boyd, Professor of Veterinary Medicine of the University of Minnesota, in this feature of the experiments.

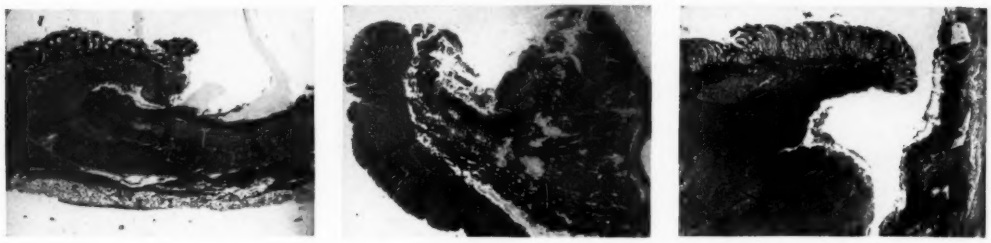

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Fig. 5. Histological sections of histamine ulcers (×8). a (Table I, Dog No. 2. Fig. 2d.), There is a large area of excavation in the pyloric antrum of the stomach, also thickening of the external serous coat of the stomach. b (Table III, Cat No. 1). Section cut in juxtaposition to area of perforation. c (Table VI, Pig No. 2), This section was obtained from the indurated edge of an undermining ulcer.

injections of aqueous solutions of histamine are absorbed rapidly and the effects are of relatively short duration. A prompt response from gastric pouches attends such injections of histamine in dogs, but the effect does not persist for more than 1½ to 2 hours (Fig. 1a). When histamine is placed in the beeswax mixture a prolonged continuous secretion of gastric juice is evoked. This response has been studied quantitatively by Code and Varco, using dogs with Heidenhain pouches of the stomach. During the present investigation, this extended action of histamine in beeswax has been verified repeatedly. The intramuscular injection of a properly prepared beeswax mixture, containing 15 to 60 milligrams of histamine base is followed within 10 to 15 minutes by a flow of gastric juice. The acidity and volume of gastric juice, as collected from the Heidenhain pouches, increase for several hours and the stimulation persists, customarily, for at least 24 hours. During this period the total volume secreted, expressed as tenth normal hydrochloric acid, was usually 1 to 2 liters; the titratable free acidity was between 140 to 150 degrees for the major portion of the period (Fig. 1b). Hypochloremia and dehydration were combatted by the administration of intravenous normal solution, dilute salt water *ad libitum* by mouth, and the return of pouch secretions by gastric intubation.

Experimental production of ulcer in various animals. Following are brief summaries of our experiments:

1. Dogs. Twelve adult mongrel dogs, weighing from 17 to 40 pounds were given 30 milligrams of histamine base daily, and 11 of these developed ulcers, 87 per cent (Table I). Eight animals had duodenal ulcers and in 4 of these the ulcers were multiple. Three dogs showed gastric ulcers. The gastric ulcers occurred in the usual location, on the lesser curvature of the stomach. The duodenal ulcers occurred in the first part of the duodenum (Fig. 2). In general, it can be said that the size of the ulcers varied directly with the length of time over which the daily injections were made; however, there was no absolute correlation between histamine dosage and size of the ulcer. Though mongrel dogs whose age was not known were used, the younger appearing animals seemed more readily susceptible to ulcer formation; that is, the ulcers developed more quickly, as a rule. In the instance of the last dog shown in Table I (No. 13) the three largest gastric arteries were ligated several weeks before injection and still ulcers developed following the administration of the histamine-beeswax mixture. Three of the dogs were pregnant throughout the period of injection (Table I, Dog Nos. 10, 11, 12). No evidence of ulcer formation was observed in the fetuses.

2. Guinea pigs. Eight guinea pigs were injected daily with beeswax mixture containing 5 milligrams of histamine base (Table II). Six of the 8 developed definite ulcers; 4 had duodenal ulcers; 1, a gastric, and 1 had both. One of the remaining 2 animals was killed accidentally on the fifth day, and exhibited no evidence of ulcer formation. The other expired during the night and though no duodenal ulcers were present, the stomach had undergone such marked postmortem autolysis that gastric ulcer could not be ruled in or out. Two control guinea pigs, after receiving the same amount of beeswax and mineral oil daily for a longer period (15 days) than any of the animals in the series, showed no ulcers.

3. Cats. The experimental production of ulcer in cats, employing the histamine-beeswax mixture, has been reported previously. In that series, 8 cats were injected. Ulcers or erosions were observed in all the animals. In the present study, 5 cats were injected with varying amounts of histamine in an effort to determine the minimal dose required for ulcer formation (Table III). The 4 cats, receiving from 5 to 15 milligrams of histamine base daily, developed

TABLE III.—PRODUCTION OF ULCER IN CATS WITH HISTAMINE-BEESWAX MIXTURE

Cat No.	Size	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	Adult	15	16	Perforated gastric ulcer	Expired, peritonitis
2	Adult	5 q. 2 da.	28	No definite ulcer	Sacrificed. Several punctate erosions in antrum
3	Adult	5	28	One ulcer and 2 erosions in duodenum	Sacrificed
4	Adult	10	3	Three ulcers in antrum	Expired, pneumonia
5	Adult	10 q. 2 da.	21	Three gastric ulcers	Expired, pregnant

TABLE IV.—PRODUCTION OF ULCER IN CHICKENS WITH HISTAMINE-BEESWAX MIXTURE

Chicken No.	Size	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	1 lb. young	7.5	4	Ulcer in gizzard	Sacrificed
2	1 lb. young	7.5	4	Ulcer in gizzard	Sacrificed. Many erosions throughout gizzard
3	1 lb. young	7.5	9	Several ulcers in gizzard	Sacrificed
4	1 lb young	Equal amount of beeswax and mineral oil	9	No ulcers	Control

TABLE V.—PRODUCTION OF ULCER IN DUCKS WITH HISTAMINE-BEESWAX MIXTURE

Duck No.	Size pounds	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	6	20	20	Ulcer in gizzard, perforated ulcer in duodenum	Expired, perforation
2	6	20	26	Four gizzard ulcers	Sacrificed

TABLE VI.—PRODUCTION OF ULCER IN SWINE WITH HISTAMINE-BEESWAX MIXTURE

Swine No.	Size pounds	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	26	40	14	Large ulcer around esophagus. Erosion at pylorus and in duodenum	Large ulcer had perforated onto pancreas and peritoneal cavity
2	25	40	15	Large perforated ulcer around the esophagus	Perforated into localized abscess
3	25	40	13	Large ulcer around esophagus. Hemorrhagic erosion on greater curvature	Several erosions in antrum

TABLE VII.—PRODUCTION OF ULCER IN WOODCHUCK WITH HISTAMINE-BEESWAX MIXTURE

Woodchuck No.	Size	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	Adult	15	28	Cluster of ulcers in cardia	Sacrificed
2	Adult	20	5	Two perforated kissing duodenal ulcers	Sacrificed—peritonitis
3	Adult	20	30	No ulcers	Sacrificed. Antrum shows mammillations and 5 punctate erosions

ulcers (Table III). Cat No. 2, after receiving 5 milligrams every other day for 28 days (14 injections) showed no definite ulcers though several punctate erosions in the antrum were noted. One of the cats (No. 5) was pregnant throughout the period of injection.

4. Chickens. Three young male chickens received injections of 7.5 milligrams into the subcutaneous

TABLE VIII.—PRODUCTION OF ULCER IN CALF WITH HISTAMINE-BEESWAX MIXTURE

Calf No.	Size pounds	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	Approx. 100	100	1	No ulcers	Two submucous hemorrhages. Expired pulmonary edema probably from histamine
2	Approx. 125	40	28	Antrum with no rea ulcers	Sacrificed. Antrum shows 20 erosions 2 to 4 mm in diameter
3	Approx. 125	30 to 75	30	Two active duodenal ulcers, 2 healed antral ulcers	Sacrificed, many erosions in antrum
4	Approx. 150	35 to 150	50	1 pyloric ulcer and 2 small antral ulcers	Sacrificed, 8 hemorrhagic erosions in antrum

TABLE IX.—PRODUCTION OF ULCER IN MONKEY WITH HISTAMINE-BEESWAX MIXTURE

Monkey No.	Size pounds	Daily dose of histamine base milligrams	No. of injections	Results	Remarks
1	6½	20	29	No ulcers	Exploratory gastrotomy and duodenotomy
2	8	40	29	No ulcers	3 submucosal hemorrhages 3–5 mm. in diameter and superficial erosion 6 mm. in diameter in fundus
3	7¾	40	59	No ulcers	On lesser curvature above angulus are erosions 4 and 7 mm. diameter; 5 other small erosions
4	7	50	23	Gastric ulcer	Sacrificed

TABLE X.—PRODUCTION OF ULCER IN RABBIT WITH HISTAMINE-BEESWAX MIXTURE

Rabbit No.	Size	Daily dose of histamine base milligrams	No. of injections	Results*	Remarks
1	Adult	30	16	No ulcers	Sacrificed
2	Adult	30	41	Probable linear erosions of apices of rugae	Sacrificed
3	Adult	30	41	Gastric ulcer	Sacrificed
4	Adult	30	41	No ulcers	Sacrificed
5	Adult	15 7.5	17 days 16 days	No ulcers	Sacrificed. 2 small hemorrhagic erosions and 2 linear erosions
6	Adult	15 7.5	10 16	No ulcers	Sacrificed
7	Adult	7.5	5	No ulcers	Sacrificed
8	Adult	7.5	10	No ulcers	Expired after 1 week of diarrhea with round worms found in gastrointestinal tract at autopsy

*See legend of Figure 4d and section "Evaluation of Study." By discarding the cellulose pulp of cabbage, carrots, and lettuce and feeding the rabbit only the juice which went through the press, ulcer was produced quite regularly with the histamine-beeswax mixture. (Wangensteen and Lannin, Arch. Surg., 1942, 44:491.)

tissues and muscles of the back and all developed gizzard ulcers in from 4 to 9 days (Table IV). A control chicken, receiving an equal amount without histamine, failed to develop ulcer.

5. Ducks. Two adult ducks, weighing 6 pounds each, were given 20 milligrams of histamine for 20 and 26 days, respectively, and both developed deep gizzard ulcers (Table V). Duck No. 1, in addition, showed a perforated duodenal ulcer.

6. Swine. Three swine, weighing approximately 25 pounds each, received 40 milligrams of histamine daily, over a period of 13 to 15 days (Table VI). Each developed large ulcers, 5 or 6 centimeters in diameter around the entrance of the esophagus. In 2 of these (Nos. 1 and 2), perforation occurred into the peritoneal cavity. In addition, pig No. 3 showed a large hemorrhagic area with necrosis and erosion on the greater curvature. This lesion resembled an infarct—the only lesion in the series which did.

7. Woodchucks. Three adult woodchucks were given 15 and 20 milligrams of histamine daily for from 5 to 30 days. Two developed ulcers (Table VII). One of these animals had a perforated duodenal ulcer and the other a gastric ulcer. The third woodchuck exhibited mammillations of the antrum and 5 punctate erosions of the mucosa.

TABLE XI.—SUMMARY OF RESULTS: INCIDENCE OF PRODUCTION OF ULCER IN THE VARIOUS GROUPS OF ANIMALS

Animal	No. in series	Daily amount of histamine base milligrams	No. of days	No. of ulcers	Per cent
Dogs	12	30	4–37	11	87.5
Guinea pigs	8	5	2–11	6	75
Cats	5	5 q. 2 da. to 15 day	3–28	4	80
Chickens	3	7.5	4– 9	3	100
Ducks	2	20	20–26	2	100
Swine	3	40	13–15	3	100
Woodchucks	3	15–20	5–30	2	66
Calves	4	30 to 150	1–50	2	50
Monkeys	4	20–50	23–59	1	25
Rabbits	8	7.5 to 30	5–41	1	12.5*

*See footnote to Table X.

8. Calves. Calf No. 1 (3 days old), weighing approximately 100 pounds was given 100 milligrams of histamine and showed immediately, difficulty with respiration and exhibited a tendency to cough. The attack resembled that of asthma in man or "heaves" in horses. By following day, animal had expired. Autopsy revealed a moderate pulmonary edema and lungs did not collapse when thorax was opened.[1]

Calf No. 2, weight 125 pounds, received 40 milligrams of histamine for 28 days and developed no ulcers. Mammillations and many erosions, 2 to 4 millimeters in diameter, were present in the antrum.

Calf No. 3 was started on 30 milligrams of histamine per day and this was increased 5 milligrams a day until 75 milligram dose was reached. Thereafter, 75 milligrams daily was given. Two active duodenal and 2 healed antral ulcers were found at autopsy.

Calf No. 4, weighing 150 pounds, was started with 35 milligrams of histamine and this was increased 10 milligrams per day until 150 milligram dose was given daily, for the remainder of 50 days. Two small antral and 1 pyloric ulcer were found at autopsy.

9. Monkeys. Four monkeys were injected (Table IX). Monkeys 1, 2, and 3 each received 20 milligrams of histamine daily for 29 days. All appeared in good health at the end of this period. Duodenotomy and gastrotomy on monkey No. 1 showed no abnormalities. Injections were discontinued, therefore. In monkeys 2 and 3, daily injections of 40 milligrams of histamine were made for 29 and 59 days, respectively; no real ulcers resulted. Superficial erosions were noted, however, in both monkeys. Monkey 4, which had received no previous histamine injections was then given 50 milligrams daily, for 23 days and developed a chronic gastric ulcer.

10. Rabbits. Eight rabbits were given 7.5 to 30 milligrams of histamine in beeswax for from 5 to 41 days and ulcers were obtained in only 1 instance (Table X). It will be noted that 1 of the 3 rabbits receiving 30 milligrams daily for 41 days developed a gastric ulcer. The linear erosions mentioned in Table X were defects along the apices of the rugae.

More recently, mindful of how difficult it is to provide an empty stomach in the rabbit, the cabbage, carrots, and lettuce constituting its diet, have been put through a press. Two rabbits were fed only the vegetable juice. A perforated duodenal ulcer was produced in one, and a long linear perforation along the great curvature, in the other.

[1]The batch of histamine beeswax mixture from which this dose of histamine was given was later found to be defective due to the use of moist histamine dihydrochloride which apparently allowed a rapid absorption of the histamine from the mixture.

PATHOLOGY OF EXPERIMENTALLY PRODUCED ULCERS

Distribution. By location, the ulcers produced in various animals by the histamine-beeswax injections distributed themselves as follows: 18 were in the stomach; 15 in the duodenum, and, in 3 instances, both gastric and duodenal ulcers were present. In the fowl, the usual location of the ulcer was the nonacid secreting mucosa of the gizzard, the homologue of the gastric antrum. In the 3 pigs injected, all the ulcers developed about the esophagus. The pig's stomach exhibits an area of squamous cell epithelium about the cardiac orifice of the esophagus. It appears likely that this epithelium may be more vulnerable to chemical injury than the glandular portion of the mucosa.

In 18 instances the ulcers were multiple; in the 15 remaining instances, a single ulcer was found.

Gross appearance of the ulcers. On the whole, these experimentally produced ulcers resemble closely those occurring spontaneously in man.

In the main, two types of ulceration were observed: (1) Acute ulceration, accompanied usually by perforation and unattended by induration of the tissue immediately adjacent to the ulcer. In other words, these ulcers exhibited perforation with little or no change in the tissues, peripheral to the ulcer. (2) Chronic ulceration, with thickening of all the tissues of the wall adjacent to the ulcer. Calloused ulcers with extreme induration were observed in the pigs, and, as before indicated, the ulcers in all 3 of the pigs occurred in juxtaposition to the esophagus. Yet perforation of the gastric wall, onto the pancreas, was observed in 2 of the 3 pigs. Most of the other indurated ulcers occurred in the antrum of the stomach. The edges of the chronic ulcers were demarcated sharply, as a rule, with elevation of the surrounding indurated tissues. The base of such ulcers was covered often with a gray exudate; in several instances there was old blood on the floor of the crater. In the dog, followed with more care than the other animals in the series, blood was noted often in the stool and decline of the hemoglobin was usual.

Microscopic appearance. As yet, a thorough histological study of the stomach of animals in which ulcer was produced by histamine has not been completed. Whether such ulceration formation is accompanied by an extensive interstitial infiltration of lymphocytes of the antrum as attends spontaneous ulcer in man, as a fairly constant accompaniment, has not been determined yet. The appearance of the edge of an experimentally produced ulcer is shown in Figures 5a, b, c, for the dog, cat, and pig, respectively.

PREVIOUS ATTEMPTS AT THE EXPERIMENTAL PRODUCTION OF ULCER WITH HISTAMINE

Buechner and Molloy (1927) succeeded in producing erosions and ulcerations in the proventriculus of rats by injecting subcutaneously, an aqueous solution of .06 gram of histamine per 100 grams of body weight. Buechner, Siebert, and Molloy (1928) elaborated upon these findings, pointing out that starving the animals on alternate days increased the incidence of erosions and ulcers. Buerkle de la Camp (1929) confirmed the work of the previously named authors and obtained the greatest incidence of erosions by injecting the histamine solution 3 times daily, also starving the animals on alternate days. In a footnote on page 49 of his paper, Buerkle de la Camp directs notice to the spontaneous occurrence of ulceration in the proventriculus of rats. The incidence of this spontaneous occurrence, however, is considerably less than the quite constant appearance of erosions and ulcerations, noted by Buerkle de la Camp after histamine provocation. In our laboratory, observation of such spontaneous occurrences of erosions and ulcers in the proventriculus of the rat dissuaded us from employing that animal as a test subject.

Matsueda (1931) failed to produce erosions or ulcers in rabbits, dogs, and guinea pigs with injections of large single doses of histamine. When, however, he began with 0.3 to 1 milligram of histamine per kilogram of body weight and increased this dose to 1 to 3 milligrams per kilogram, giving 3 injections a day, Matsueda succeeded in producing erosions and ulcers in the 3 types of animals in which he had failed previously with single injections. Matsueda shows a photograph of a perforated ulcer in the fundus of the rabbit.

Harde (1932) produced erosions in the stomachs of mice and in a few instances in guinea pigs by subcutaneous injection of small doses of aqueous histamine. The mice were each given 0.25 milligram and the guinea pigs and rabbits 1 milligram of histamine each, per day. Harde failed to produce gastric erosions in the rabbit.

Eppinger and Leuchtenberger (1932) produced shock in dogs by single intravenous injections of large doses of histamine (30 to 60 milligrams). In 4 such animals gastric erosions were observed. In 1, the authors describe the presence of an ulcer, though their Figure 4, shown to illustrate its occurrence, demonstrates excavation as occurring only to the muscularis mucosae—the usually accepted definition of an erosion as contrasted with an ulcer in which the excavation extends into the circular muscle layer of the stomach or duodenum.

Orndorff, Bergh, and Ivy (1935) in a paper entitled "Peptic Ulcer and Anxiety Complex; Failure of Pharmacologically Sustained Hy-

persecretion and Hypermotility of Stomach to Produce Chronic Gastric Ulcer in Dogs" carried out a most diligent attempt to provoke ulcer formation with histamine. Ten dogs were injected subcutaneously with 2 milligrams of aqueous histamine every 2 hours, day and night, 10 times a day, the dogs being allowed a 4 hour rest period daily. These injections were continued daily for a period extending up to 66 days. Among 4 of the 9 dogs which survived the experiment, superficial erosions were noted in the duodenum.

Heinlein and Kastrup (1938) failed to produce erosions or ulcers in cats with subcutaneous injections of histamine, but did succeed in producing an interstitial submucosal lymphocytic infiltration, which they describe as a gastritis.

McIlroy (1928) reports that he noted the presence of 2 well defined ulcers in the stomach of 1 of 4 cats which had received injections of histamine. This observation led him to attempt to determine whether the administration of histamine would delay healing in gastric mucosal defects created by operation. McIlroy believed, as a result of experiments upon 7 cats, that the healing time, as compared with controls, was prolonged definitely.

O'Shaughnessy (1931) injected histamine locally into the gastric wall of cats and administered histamine subcutaneously twice daily and succeeded in producing 2 chronic ulcers out of trials on 90 cats.

Flood and Howes (1934) undertook a study somewhat similar to that reported previously by McIlroy, on both cats and dogs, using relatively smaller doses than McIlroy. Flood and Howes noted definite delay in healing in previously established antral mucosal defects with histamine administration; no delay in healing of defects high along the greater curvature attended subcutaneous administration of histamine.

EVALUATION OF STUDY

A means by which typical ulcers, not unlike those occurring in man, may be produced quite regularly, in a number of the common laboratory and domestic animals, is described. No ulcers appeared in our control animals to which a beeswax-mineral oil mixture was administered, omitting the histamine. Nor have we observed the occurrence of spontaneous gastric or duodenal ulcer in dogs and cats in this laboratory. Turck (1916) noted no instances of ulcer in 189 healthy and 82 diseased dogs. Mann (1916) failed to observe the spontaneous occurrence of ulcer in 200 normal dogs and cats. Ivy (1920) observed a pyloric ulcer once in examining the stomachs and duodena of 900 dogs.

Animals vary considerably, with reference to the ease or difficulty with which ulcer may be produced by the intramuscular injection of histamine in beeswax. The guinea pig and cat are probably most susceptible to the development of ulcer formation with histamine stimulation. The monkey and the rabbit are probably the most refractory. Yet, recently, in the rabbit, by employing a diet which would facilitate gastric emptying, ulcers were produced readily by histamine stimulation. Similar studies may afford clues concerning the apparent refractoriness of some animals to the production of a histamine ulcer. It is interesting to note that pregnancy appears to be no deterrent to the experimental production of ulcer by histamine stimulation.

The predominating action of histamine on the gastric mucosa is the stimulation of the acid producing cells. Histamine gives a gastric juice with maximal acidity. It does not give a maximal stimulus to the secretion of pepsin and mucus. It seems highly probable that it was this highly acid gastric juice acting, more or less continuously, over a prolonged period which produced the ulcers in the stomach observed in this study. Likewise, the ulcers in the duodenum seem, most certainly, to have been produced by the overwhelming effects of a prolonged excess of acid gastric juice. Histamine may not afford the same stimulus to the flow of bile, pancreatic juice, and duodenal secretion as it does to the production of acid gastric juice. Thus, an unequal stimulation of those agents which normally counteract and neutralize hydrochloric acid may have contributed toward the production of the ulcers seen in this study. It seems most likely that the acid, inadequately opposed, produced digestion of the gastric or duodenal wall with resulting ulcer formation and all the associated

complications such as serious hemorrhage or perforation as may be seen in ulcer in man.

The regularity with which ulcer may be produced experimentally with histamine lends strong support to the thesis that acid is *the important factor* in the genesis of spontaneous ulcer in man. The production of ulcer, by stimulation of the intrinsic mechanism for the secretion of acid, indicates how important an item the effective control of gastric acidity is, in the management of ulcer. The method described herein, of producing ulcer is proving, in our hands, a very satisfactory instrument to assess the capacity of any operation to prevent ulcer recurrence (12) (see Fig. 2c).

SUMMARY AND CONCLUSIONS

A method is described by which a prolonged maximal secretion of hydrochloric acid may be provoked from gastric pouches of dogs. This method consists in embedding histamine in beeswax, to permit gradual liberation of the histamine on intramuscular injection of the mixture. With employment of this agency, gastric and duodenal ulcer may be produced with some regularity in a number of common laboratory and domestic animals. These ulcers lend every appearance of being not unlike the ulcers which occur spontaneously in man.

The experimental production of ulcer, in this manner, furnishes additional testimony to the great importance of acid in the genesis of ulcer. This method of producing ulcer experimentally provides a simple means of evaluating the worth of therapeutic agents in retarding or influencing favorably the healing of ulcer. In addition, it affords the surgeon a method of determining, experimentally, what operative procedures performed upon the stomach for the relief of ulcer may thwart the ulcer diathesis and obviate recurrence of ulcer after operation.

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WAR INJURIES TO ARTERIES AND THEIR TREATMENT

EMILE HOLMAN, M.D., F.A.C.S., San Francisco, California

IN October, 1941 (14), the writer stated: "The imminent threat of American participation in World War II prompts me to present a review of the treatment of gunshot injuries to the peripheral arteries, together with a brief report of the experiences of military surgeons as recorded in recent European literature." The need for such a review is obviously even greater today. Moreover, many of the lessons learned in war time are directly applicable to the injuries of civil life, particularly to those sustained in areas remote from immediate hospital care.

In describing arterial injuries, both English and French writers report a "concussion" or "*stupeur*" of an artery, producing a localized, segmentary spasm, which may disappear within 24 hours. The affected segment appears normal on excision. Such a spasm may even occur as a result of a wound in the vicinity of the artery, without demonstrable injury to the artery itself, and may be sufficiently active to cause the distal pulse temporarily to disappear. Treatment consists of a débridement of the surrounding traumatized tissue and a periarterial sympathectomy above and at the site of spasm.

A second type of injury is a localized contusion, a sequel of which may be thrombosis at the site of injury, which may, by extension distally or by the liberation of an embolus initiate massive gangrene. Another sequel may be necrosis of the contused wall and secondary hemorrhage, either externally through the wound, producing shock or death, or into the tissues around the arterial lesion, producing a pulsating hematoma. If untreated, this may eventually lead to the formation of a sacculated aneurysm. Should artery and vein both be involved in the contusion, a varicose aneurysm may be a late development.

As to the treatment, one of the rules in the official history of World War I reads:

"When a large vessel is exposed in an open wound, and has obviously suffered contusion and is thrombosed, the vessel should be ligated above and below the thrombosed segment and the latter excised." Such excision removes the danger of embolism, of secondary hemorrhage, and eliminates the vasoconstrictor influences affecting the vessels beyond the injury.

A second rule was enunciated in 1939 by Maurer, the French surgeon: "If the path of a projectile seems to have crossed a vessel area, it is necessary to expose the vessels and verify the absence or presence of injury." Disregard of this rule may occasionally be permitted as in bullet injuries with small wounds of entrance and exit, particularly when no clinical evidence of injury to the vessels is present, such as a pulsating hematoma or a cadaveric limb with no pulse palpable beyond the injury.

The immediate treatment of injuries to large vessels depends upon the severity of the bleeding and upon associated injuries to other structures. The loss of large masses of tissue may require immediate amputation to save life. In less extensive injuries, if transport facilities are good and distances not too great, provisional arrest of hemorrhage with a compression or Esmarch bandage may be undertaken, but when prolonged transport is necessary, immediate ligation of bleeding vessels may be mandatory.

First aid treatment must, of course, be prompt and efficient. Occasionally, as with venous bleeding, application of local pressure to the wound by means of a sterile dressing may be all that is necessary. First aid stations should be liberally supplied with sulfathiazole powder for introduction into the freshly made wound. At the first aid station also, instructions and material for the oral administration of sulfathiazole every 2 to 4 hours during the period of transportation should be provided. The soldiers themselves should carry with them packets of sulfathiazole containing:

Lieutenant Commander, Medical Corps, U. S. N. R.
From the Department of Surgery, Stanford University Medical School, San Francisco.

(a) 10 tablets of 1 gram each, 4 to be taken by mouth at time of injury, and 1 every 4 hours thereafter; (b) 3 to 5 grams of the powder form to be introduced into the wound itself, whenever possible, on the battlefield immediately after the injury while transportation is awaited.

When a tourniquet is found necessary, it must be tied tightly enough to compress the artery, but no tighter. If tied too loosely, the artery may be partially open and the veins completely blocked, thus resulting in increased rather than decreased bleeding. Tourniquets below the knee or below the elbow are contraindicated, since the two bones prevent complete control of the interosseous arteries. Intractable and copious bleeding at the wrist has completely ceased following the removal of a tourniquet on the lower arm. As Mitchiner, the English surgeon, suggests, the exact time and fact of the application of the tourniquet must be recorded on the patient's forehead, a strip of adhesive being used. As the patient is being transported to the rear, the tourniquet must be loosened when possible and feasible every hour, and the fact and time so recorded on the forehead.

The experiences of Allen and Brooks with the survival of tissues deprived of their blood supply and cooled to 5 degrees C., prompts the suggestion that if ice could be made available from refrigerating units near the front line, such tourniquetted limbs should be packed in ice bags before and during transportation. The tourniquet could then remain in place for 5 to 6 hours without harm to the tissues. Moreover, the reduced temperature of the injured limb provided by packing in ice bags would also have the effect of inhibiting bacterial growth in the wound, of reducing shock imposed by injured tissues, and of providing absolute comfort during transportation. An additional advantage of great importance would be the possibility, after 3 to 5 hours of being packed in ice, of performing a débridement on arrival at an evacuation hospital without the necessity of anesthesia. Tissues deprived of their blood supply and cooled to 5 to 7 degrees C. are anesthetic to pain. Such débridement must be particularly thorough following such refrigeration. Every precaution should be taken at the time the tourniquet is applied to have all recesses of the wound well impregnated with sulfonamide powder to ensure complete inhibition of all bacterial growth.

Bleeding from wounded arteries is governed by many diverse factors. A tangential wound in an artery usually bleeds interminably to the death of the animal, whereas a completely severed artery will bleed profusely for a few moments and then cease entirely as the elasticity of the arterial wall gradually withdraws the vessel from the site of injury and envelops the severed end in a mass of adventitia (Fig. 1). For example, a tangential wound of the left femoral artery in animal 1 bled for 20 minutes until the death of the animal; whereas a completely divided right femoral artery in the same animal bled only 5 minutes. The amount of blood lost from the incompletely severed left artery was 105 cubic centimeters, but only 45 cubic centimeters were lost from the completely divided right artery. In animal 2 a tangential wound of the right femoral artery bled 7 minutes to the death of the animal with the loss of 300 cubic centimeters of blood. The completely severed left femoral artery bled only 2 minutes with the loss of a paltry 30 cubic centimeters of blood (Fig. 1). The would-be suicide frequently fails because he completely severs the radial artery, whereas a partially severed artery might have accomplished his purpose.

Suturing of the wounded artery is considered by many surgeons, including von Haberer, as definitely indicated (when possible) in injuries of the larger vessels such as the common carotid, subclavian, axillary, brachial, common, and external iliac, femoral, and popliteal arteries. Suture should *not* be performed in those instances in which the artery can be permanently ligated without harm, as for example the external carotid, either radial or ulnar arteries, and anterior or posterior tibial arteries. Mitchiner warns that reparative surgery, even of large vessels, has a very limited field. He states: "Under war conditions, the results of such reparative vascular surgery are notoriously disappointing. The tyro or inexperienced surgeon is apt to spend unavailingly much precious time in

attempting the repair of vessels better ligated. It may be questionable in the rush of a casualty hospital if it is justifiable to take considerable time over an operation on one subject, the results of which are considerably in doubt, while many other urgent cases call for prompt attention from the surgeon."

Mitchiner further observes that in the last war, in approximately two-thirds of the cases in which repair operations were employed, thrombosis occurred at once, although not one of these limbs was lost. The remaining one-third of the cases maintained their circulation through the site of operative repair. However, 3 years later, those patients in whom repair was accomplished, but whose vessels had thrombosed, were well and working; whereas almost all those in whom immediate suture had been successful now had aneurysms at the site of operation, requiring ligation of vessels and excision of the sac before a useful limb was obtained.

Such observations are, indeed, discouraging as to the value of ever attempting the repair of an injured vessel. A small, cleancut, longitudinal laceration, or a transverse cut involving less than one-third of the circumference of the artery might be advantageously sutured. The local application of the sulfonamides might be expected to reduce postoperative thrombosis, thus averting some of the objections voiced by Mitchiner. It need not be pointed out that conditions for such arterial suture must be as perfect as possible: absolute asepsis, proper instruments and facilities and the availability of heparin, continuously administered for at least 24 hours after the operation, to reduce postoperative thrombosis at the site of suture. Unless ideal conditions prevail, it would seem preferable to control bleeding by ligation of the injured artery at once, particularly if the laceration is a jagged one or if loss of substance makes an end-to-end suture necessary. Such ligation should be performed at two points above and below the injury, and the artery completely divided. Double ligation and complete division is preferable to ligation in continuity since erosion of the vessel wall at the site of ligation is always a real danger when a large artery is ligated in continuity. Complete

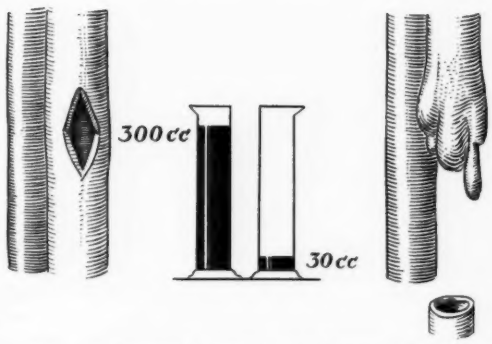

Fig. 1. A tangential wound in right femoral artery bled 300 cubic centimeters in 7 minutes to death of animal; whereas the completely severed left femoral artery bled only 2 minutes with loss of only 30 cubic centimeters, due to retraction and envelopment of the severed end in a mass of adventitia.

division permits retraction and shortening of the vessel due to its elastic elements, thus producing a thickened vessel wall. This was shown experimentally (12) by double ligation of the abdominal aorta in a dog and division between the ligatures. The two ends retracted until they were separated 3.8 centimeters with perceptible thickening of the proximal aortic wall. It was evident, as one observed the pulsating proximal end, that the force of each pulsation was distributed over a wide area and was dissipated in expanding and lengthening this thickened blind end (Fig. 2). When ligation of the abdominal aorta was performed in continuity, it was equally evident that the maximum force of each pulsation was concentrated at the site of ligation, which, being a fixed point resulted in a widening and expansion of the vessel wall only, and not in its lengthening. The constant battering of the pulse beat against the fixed point of ligation leads first to microscopic and molecular rupture of cells, followed by a gradual macroscopic erosion of the vessel wall.

Ligation in continuity also invites reopening of the vessel lumen at the site of ligation. A ligature tied sufficiently tight to occlude an artery and shut off flowing blood will cause necrosis of all the tissues included in the ligature (Halsted). Envelopment of the ligature and its included tissues in exudate, fibrin, and eventually fibrous tissue, usually

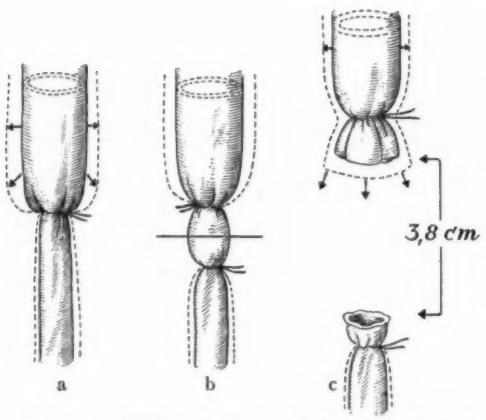

Fig. 2. a, Ligation in continuity invariably leads to necrosis of the included vessel wall, and rupture if the vessel is large, due to constant battering of the blood stream against a fixed point. b and c, Ligation and division leads to marked retraction of the proximal stump, thickening of the vessel wall. The force of each pulsation is dissipated in both lengthening and widening of the vessel, and as this force is not concentrated at site of ligation the danger of rupture is almost nil, regardless of size of vessel.

prevents fatal rupture. Occasionally, necrosis of tissue may lead to partial cutting through of the ligature, resulting not always in perforation, but more frequently in partial restoration of the artery—a disappointing sequel to ligation in continuity. When ligation in continuity is found imperative, graduated ligatures paralleling the size of the artery must be used (Ballance and Edmunds; Reid, 27); e.g., tape ligatures on the aorta or innominate artery, heavy braided ligatures of silk on the iliac or subclavian arteries, and smaller braided silk on the femoral and carotid arteries.

Pearse has recently advocated the employment of unsurfaced cellophane as a desirable material to place around large arteries, instead of complete ligation with silk. The cellophane produces a circular fibrous reaction which gradually occludes the vessel. Because of recurrence of murmur and symptoms, Gross, in ligation of the patent ductus, has recently employed an encircling band of cellophane as well as two ligatures of silk to ensure permanent cicatricial closure of the ductus.

When a vessel is to be ligated and divided, the ligature need not be graduated to the size of the vessel, but needs to be only large enough to permit the tying of the ligature without its breaking. In the ligation of a large vessel, the lumen should first be emptied by stripping the artery of blood, its refilling during ligation being prevented by digital pressure on both sides of the site of ligation (Reid, 27). This ensures the application of the ligature on a relaxed vessel instead of on a fully distended vessel, thus avoiding a fracture of the walls.

A further argument against ligation in continuity is suggested by the observations of Leriche and Werquin. They believe that the severe trauma imposed upon the periarterial sympathetic plexus by the ligature produces a reflex vasoconstriction in the arterial bed distal to the ligature, thus obliterating or closing potential collaterals. Furthermore, Mitchiner observes that unless an artery is completely divided, vascular disturbances may develop years later, characterized by pain, poor pulse and claudication in the affected limb—symptoms which are completely relieved by division of the fibrous cord at the site of previous ligation or repair.

In those rare instances in which repair of a wounded artery has been attempted, the wound in the soft tissues should be closed without undue tension, the part should be elevated, and a splint should be applied to ensure rest. Such a splint should be worn at least 14 days (Mitchiner). The patient is not allowed out of bed for a month from the time of arterial suture.

The problem of whether ligation of the accompanying vein is desirable whenever a large artery is ligated for simple arterial lesions is still subject to controversy. Prompted by experiences in the early part of World War I, the Interallied Conference of Surgeons held in Paris in May, 1917, recommended that the ligation of a large artery for injury should be accompanied also by the occlusion of the satellite vein, even though the latter be uninjured.

Reichert, in ingenious replantation experiments on dogs, demonstrated that following the division of all tissues of a limb except artery, vein, bone, and nerve, and their immediate resuture, the artery alone to this replanted limb could not be ligated until the

14th day following replantation without precipitating gangrene; whereas, when the vein was ligated simultaneously with the artery, the ligation of the latter could be performed as early as the 7th day following replantation without gangrene. This evidence, amid the welter of many inconclusive experiments (Mulvihill, Harvey, and Doroszka; and Wilson), proves beyond the slightest doubt the beneficial effect produced upon the nutrition of a limb by the simultaneous ligation of artery and vein.

In a clinical study by Sehrt, it was found with reference to the lower extremity, that ligation of the artery alone was followed in 20 per cent of his cases by gangrene; whereas ligation of both the artery and vein was followed in only 9 per cent by gangrene. With reference to the upper extremity he found that ligation of the artery alone resulted in gangrene in 7.8 per cent of the cases, and that ligation of both artery and vein resulted in no gangrene. He attributes the larger incidence of gangrene in the lower extremity to the absence of large muscle masses bridging the knee as compared with those bridging the elbow.

In a statistical summary by Heidrich, we find that among 995 ligations of the large arteries alone, gangrene occurred 154 times—a percentage of 15.5—and among 198 ligations of both artery and vein, gangrene occurred 17 times—or a percentage of only 8.5.

With these facts before us, there would seem to be no doubt that ligation of the vein is indicated whenever one of the large arterial trunks requires ligation.

An exception to this rule occurs in the presence of the so called Henle-Coenen phenomenon (Pemberton): If, following ligation and division of an artery, the distal arterial stump is seen to pulsate, (conclusive evidence of adequate collateral circulation) the vein need not be ligated. If no such distal pulsation is observed or felt, the vein should also be ligated.

A false or sacculated aneurysm is not infrequently encountered as a later development of simple arterial injuries. Ligation of the vessel above and below the lesion with extirpation of the sac when feasible is an acceptable procedure, accompanied usually by ligation also of the accompanying vein. Restoration of the artery by suturing of the rent according to the method of Matas is the operation of choice when technically possible.

Injuries producing direct communications between artery and vein are particularly inimical to the later health of the patient. The diagnosis of such a lesion is usually quite simple. The injury is accompanied by profuse but easily controlled bleeding, and by the prompt development of a thrill and bruit continuous throughout the cardiac cycle. Occasionally, the appearance of the thrill and bruit is delayed for several hours, or even days, due probably to the temporary occlusion of the abnormal communication by a blood clot. If sufficiently large, the fistula will ultimately lead to profound circulatory effects: namely, dyspnea and tachycardia on the slightest exertion, an increasingly vigorous beating or "pounding" of the heart, a slowly developing decompensation due to a dilating heart, followed inevitably by complete invalidism and death. In several patients, extraordinary momentary faintness, relieved by sitting or falling down, has been observed—a symptom referable to a failing circulation. In addition, there may follow in the wake of a fistula various local manifestations, such as edema, often elephantiasic in type, marked varicosities complicated by eczema and ulceration, and occasionally gangrene.

With these possible developments before one, there can be little doubt that a fistula must be eliminated from the circulation. If seen immediately after the accident producing an arterial injury, the patient should be placed in a hospital for observation. If, under bed rest, the bleeding ceases, and there is no increase in the swelling of the limb due to an enlarging hematoma, nor evidence of developing infection, further delay in operating is advisable. On the other hand, an increasing hematoma at the site of the injury, or an increasing swelling of the limb which threatens the blood supply of the extremity beyond it, as shown by a cold, edematous, and pulseless leg, requires immediate operation. The operation is preferably done under a tourniquet, the hematoma is evacuated, a localized dé-

bridement performed, and the injured vessels exposed. In the absence of any evidence of infection, a suture of the arterial wound may be attempted. The vein is ligated to avoid the danger of an embolus either of air or blood clot. If such suture is impossible, the ligation and division of artery and vein is in order. Repeated and massive transfusions are indicated to maintain and raise peripheral arterial pressure, since this is the best guarantee that a limb deprived of its main artery will survive. Interruption of the lumbar sympathetics will encourage collateral circulation by promoting vasodilation. This may be done by novocain and alcohol injection of the lumbar or thoracic ganglia, or by direct operative interruption if the lower abdomen is opened for injuries to iliac vessels (5).

Should evidence of infection be present, the hazard to life is greatly increased. Under a tourniquet, the wound is laid wide open, blood clots are removed, a débridement is performed, the injured portions of the artery and vein are excised, and the 4 ends of the vessels are ligated. The wound is left widely open, and Dakin's solution is introduced at hourly intervals. In a contaminated, though not grossly suppurating, wound, sulfathiazole liberally employed is preferable to dakinization. Sulfonamides by mouth are given liberally.

If the wound to the artery appears trivial, and the diagnosis is not immediately made (and this is often the case), operation should be deferred until all danger of infection is over. Indeed, the observation that small fistulas heal spontaneously has led Reid (26) to advocate postponement of surgical intervention for 6 months. Experiments have shown, however, that only small fistulas tend to heal spontaneously, and that large fistulas do not (11). If, therefore, evidence develops that the heart is enlarging, that the thrill and bruit are increasing rather than diminishing in intensity, that variations in blood pressure and pulse can be produced by closing the fistula, and that these variations are becoming more, rather than less, pronounced, one may be certain that the opening will not close spontaneously and that it must be eliminated by operation to avoid further ill effects upon the circulatory system.

Reid emphasizes further that delay in operating upon a recently formed fistula is indicated so that the collateral circulation may be developed sufficiently to permit division of the artery if necessary. This delay may be as short as 5 to 6 weeks or as long as 3 to 4 months without the life of the patient being endangered. Other benefits of delay suggested by Reid are that the injured vessels become more thoroughly healed, thus making their dissection easier and safer, and infection is less likely to occur. As recorded by Mason, such delay may occasionally be accompanied by a rapid development of cardiac decompensation. In his case of a left subclavian fistula, marked symptoms of circulatory embarrassment were noted within 9 weeks after the injury which had produced the fistula. Excision of the fistula restored the heart to approximately normal function.

An important preoperative precaution in a long standing fistula is to prescribe complete rest in bed for 10 days to 2 weeks preceding the operation. Pronounced cardiac decompensation with ascites and hydrothorax may entirely disappear with simple rest (13). Digital closure of the fistula itself or of the artery proximal to the communication for 30 to 40 minutes 3 to 6 times daily will be very helpful in controlling decompensation. It will also, I believe, reduce the amount of blood flowing through the fistula by encouraging fibrous contraction about the fistula. Several patients were greatly improved before operation by this simple expedient, as shown by some diminution of the greatly dilated heart and by a definitely reduced effect upon blood pressure and pulse by closing the fistula.

Following the operative closure of a large fistula which has produced a marked dilatation of the heart, it is important to restrict activity for 6 to 8 weeks to permit the previously dilated and thinned out cardiac musculature to become readjusted to the increase in diastolic pressure brought about by closure of the fistula. An important precaution at the operating table is also related to this extreme dilatation of the heart accompanying a large fistula. Closure of the fistula not only raises diastolic pressure by an increase in peripheral resistance, but also leads

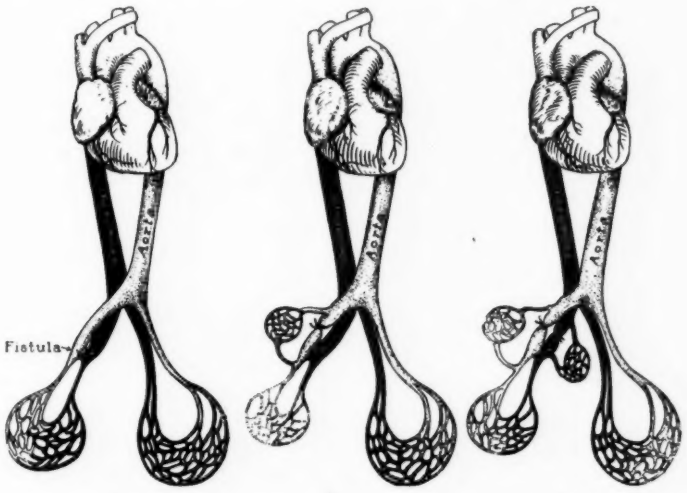

Fig. 3. a and b, Ligation of the artery proximal to an arteriovenous fistula is absolutely contraindicated, as all blood passing through collateral vessels will be diverted through the fistula back to the heart, resulting in gangrene of the part distal to the fistula. c, Ligation of both artery and vein proximal to the fistula is also contraindicated. Gangrene may not result, but the fistula remains active and is not cured. Ligation of artery and vein proximal and distal to the fistula with excision of the fistula is the treatment of choice.

to an overdistention of an already dilated heart through a redistribution of the circulating blood, more than half of which formerly leaked into the capacious venous bed. Such overdistention of an already thinned out cardiac muscle might easily lead to recurrence of the cardiac decompensation. This would be shown by an increased pulse rate and a lowered blood pressure on closure of the fistula, instead of the reverse. The operator should be prepared, should this occur, to do an immediate venesection in order to reduce the volume of circulating blood which has become considerably augmented during the lifetime of the fistula (13).

In an operation upon a fistula, certain fundamental principles must be observed. Ligation of the artery alone, proximal to a fistula, is so utterly disastrous that when confronted with an aneurysm it is most important that accurate studies be made to determine whether the lesion is a simple sacculated aneurysm or an arteriovenous fistula. Life itself may depend on the correct differentiation between these two conditions. It seems highly probable that the gangrene following ligation of an artery for a supposedly simple aneurysm has occasionally been due to the fact that the arterial injury communicated with a vein and that such a communication was not recognized.

The distinctive features of a fistula as compared with a simple aneurysm are: (a) The thrill and bruit are continuous but intensified during systole; (b) the slowing of the pulse and rise in blood pressure on digital closure of the artery proximal to the lesion occur only in the presence of a fistula and never in the presence of a simple arterial aneurysm; (c) the high oxygen content of arterial blood withdrawn from the veins distal to a fistula as compared to venous blood obtained elsewhere is a distinguishing feature suggested by Brown.

If the venous communication is overlooked, and the usual Hunterian ligation of the artery proximal to the aneurysm is performed, gangrene beyond the aneurysm is almost inevitable. The collateral circulation will find its way, not into the capillary bed distal to

the fistula, but through the fistula back to the heart (Fig. 3).

The ligation of the artery and vein proximal to the fistula may occasionally be employed as a preliminary procedure in the hope that thrombosis will occur at the site of the fistula. Usually, the fistula is not cured, as the collateral channels will readily supply blood to the site of decreased resistance provided by the fistula. In Gilcreest's interesting case, the subclavian artery and vein were ligated proximal to a subclavian fistula with some improvement. A year later, ulceration and rupture of a large surface vein of the forearm led almost to a fatal hemorrhage. The thrill and bruit were present as before, the arm was still swollen, and the veins were still enormously dilated. Ligation of the artery and vein beyond the fistula by me was followed by complete cure.

The ligation of the artery and restoration of the vein is definitely contraindicated. This may lead to gangrene due to the great disproportion between a dilated, tortuous venous system and the meager collateral arterial circulation. The little blood that passes through the collateral arterial bed finds its way promptly into the dilated venous bed, without flowing into the distal arterial bed.

In the surgical treatment of long standing fistulas, transvenous or transsaccular aneurysmorrhaphy may be attempted. Under a tourniquet, the varicose sac or the dilated vein is boldly opened, and the rent in the artery is closed by suture. The vein should be ligated above and below the fistula. The wall of the vein may be employed to reinforce the sutured rent in the artery.

Ligation of the artery and vein proximal and distal to the fistula, with excision of the fistula, is the operation of choice and the one most easily executed. An artery that is full of blood and pulsating is so much more easily identified than a collapsed vessel that isolation and mobilization of the vessels is best accomplished *without* a tourniquet, the artery proximal to the fistula being isolated first for closure in case of bleeding. If feasible, one should be prepared to apply a tourniquet at any time in the course of the operation. If not, the artery distal and proximal to the fistula or to the aneurysmal sac must be exposed first for control with a temporary ligature. Should complete mobilization and excision of the fistula be impossible because of involvement of important structures such as nerves, ligation of the artery and vein proximal and distal to the communication is in order. Under such conditions, however, the artery proximal to the fistula should be ligated *and divided* to avoid reactivation of the fistula by the reopening of the artery ligated in continuity, through necrosis of the tissues included in the ligature.

Our discussion so far has been directed mainly to a consideration of the effect of ligating the large vessels leading to the extremities. There remains also the question of ligation of the common or internal carotid artery. This procedure is frequently followed by a hemiparesis of the opposite side, due to nutritional disturbances in the cerebrum (31). Additional clinical phenomena that have been observed following ligation of these carotid vessels are convulsions, drowsiness, coma, cardiac and respiratory irregularities, fall in temperature, blindness, diplopia, and motor and sensory losses on the opposite side. Pilz gathered together 600 cases of ligation of the common carotid artery, 32 per cent of which presented cerebral symptoms.

Arguing by analogy from the better results obtained in ligation of both vessels in the extremities, Makins very emphatically advised occlusion of the jugular vein whenever ligation of the common or internal carotid arteries is considered. I have followed this rule in two ligations of the common carotid and in two ligations of the internal carotid without the development of cerebral symptoms, even in a patient 68 years of age. Halsted held that ligation of the common carotid artery could be performed with impunity in the young, and that the incidence of cerebral disturbances following ligation of the common carotid increased with age.

It is important to note also that Thompson presents evidence indicating that when circumstances demand ligation of the innominate artery, it is well to ligate also the common carotid artery. He found that only 41 per cent of 17 cases recovered following ligation

of the innominate alone; whereas 66 per cent of 12 cases recovered following ligation of both the innominate and carotid arteries. He contends that ligation of the carotid artery is indicated because "it diminishes still further the flow of blood through the aneurysm and thereby promotes consolidation, and it prevents an excessive drain of blood from the circle of Willis, thus avoiding cerebral anemia." The ligation of both carotid and innominate arteries would probably increase the percentage of subsequent gangrene in the limb unless the innominate or subclavian vein were also ligated.

The success of operations upon the large vessels depends in great measure upon the avoidance of sepsis. The strictest precautions against infection must be followed throughout, particular attention being paid during a prolonged operation to exclude the skin from the operative field. The liberal use of the sulfonamides locally and systemically is indicated in any contaminated or potentially infected wounds. Drainage in vascular surgery must be scrupulously avoided. It cannot be too emphatically stated that in surgery of the large vessels, the *packing* or *drainage* of wounds is inviting almost certain disaster. Should the wound at any time following operation fill up with fluid, it is a simple matter to evacuate it under strictly sterile precautions.

SUMMARY

1. In *concussion* of an artery localized segmentary spasm may occur which may disappear spontaneously in 24 hours. Treatment consists of débridement of surrounding traumatized tissue and a periarterial sympathectomy proximal to the spasm.

2. In *contusion* of an artery localized thrombosis and subsequent embolism may occur resulting in distant gangrene. Or the contused artery may rupture producing shock, or death, from secondary hemorrhage. Or a pulsating hematoma may follow late rupture and hemorrhage into surrounding tissues, leading eventually to the formation of a sacculated aneurysm. Treatment consists of exposure of the artery, and if contused, ligation above and below the contusion is indicated with excision of the contused or thrombosed segment.

In extensive injuries, immediate ligation of large vessels may be mandatory, if prolonged transport is necessary. If transport facilities are good, bleeding may be controlled with Esmarch tourniquet. The wound itself should be well impregnated with sulfathiazole powder, accompanied by the oral administration of sulfathiazole. If ice is available a tourniquetted limb should be surrounded by ice bags and cooled to 5 degrees C. Such a cooled limb may remain tourniquetted for 7 to 10 hours without endangering its viability. Such cooling reduces shock, inhibits bacterial growth, ensures comfort during transportation, and permits débridement without anesthesia on arrival at hospital.

Bleeding from a completely severed artery may be trivial due to retraction of vessel. A tangential wound of even a small artery may bleed interminably to death.

The suturing of a wounded artery is notoriously disappointing because of immediate thrombosis. Should the suture on rare occasion be successful, the late development of aneurysm and pain is the usual end-result. When suturing is attempted, conditions must be ideal, and heparin should be available for 24 hour continuous administration.

Ligation and division of large arteries is preferable to ligation in continuity due to possibility of erosion of the vessel or of reestablishment of lumen through partial necrosis of included tissues. Ligation in continuity may be followed years later by pain, poor pulse, and claudication in the affected limb, relieved by division of the fibrous cord at the site of previous ligation.

The vein accompanying a large artery should likewise be ligated if the artery requires ligation.

Injuries to both artery and vein producing a fistula may be followed as late as 25 years by cardiac dilatation and decompensation. Hence a fistula must be excised, with ligation of artery and vein proximal and distal to the communication. Ligation of artery alone proximal to a fistula is inviting the almost certain disaster of gangrene. Restriction of activity for 5 to 6 weeks is imperative follow-

ing excision of a fistula to avoid cardiac strain due to increase in peripheral resistance through elimination of the fistula.

The introduction of drains into a wound containing sutured or ligated vessels must be scrupulously avoided.

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POSTOPERATIVE THROMBOSIS AND EMBOLISM

Their Treatment with Heparin

JAMES T. PRIESTLEY, M.D., F.A.C.S., and NELSON W. BARKER, M.D.,
Rochester, Minnesota

POSTOPERATIVE venous thrombosis and pulmonary embolism are complications which always prolong the patient's convalescence and may rob him of his life, which otherwise might have been saved by a successful operation. Although neither of these complications occurs frequently, they are encountered sufficiently often to be of considerable clinical importance. Many forms of therapy have been suggested for their prevention as well as treatment, but as yet none of these suggestions has given entirely satisfactory results. Interest in thrombosis and embolism has been renewed during recent years because of various new therapeutic suggestions which have been offered. Prominent among these suggestions has been the use of heparin, which will be discussed later.

NATURE OF THE STUDY

In order to ascertain the scope of the problem with which one is confronted in the attempted prophylaxis and treatment of postoperative venous thrombosis, thrombophlebitis, and pulmonary embolism, and to learn something of the incidence and significant etiological factors of these conditions, a comprehensive statistical study was made of a large series of surgical cases (1). The records of a consecutive series of patients who underwent various surgical procedures during a 13 year period were reviewed, and the incidence of pulmonary embolism and thrombophlebitis was recorded. There were 1,665 cases of thrombosis or embolism in the entire series, or a percentage of 0.95. In this group of 1,665 cases there were 938 cases of thrombophlebitis and 897 cases of pulmonary embolism; in some cases both conditions occurred. Actually, the incidence of these complications probably is somewhat higher than these figures indicate, because some instances of mild thrombophlebitis or small pulmonary emboli undoubtedly were not recognized clinically. In the total group there were 343 cases (0.20 per cent) of fatal pulmonary embolism. Although in general the incidence of fatal pulmonary embolism is not high, the condition is of sufficient gravity when it does occur to make it worthy of serious consideration.

Relationship of type of surgical procedure to incidence of thrombophlebitis and embolism. By a determination of the relative incidence of thrombophlebitis and pulmonary embolism after various types of surgical procedures, certain factors are noted which appear to be significant in the development of these conditions (Table I). The site of operation apparently bears some relationship to the incidence of phlebitis and embolism, because operations performed on the extremities, trunk, head, neck, and thorax are followed by thromboembolic phenomena less often than are those performed within the abdomen. An observation of this type is of importance primarily because of the light which it might shed on the etiology of thrombosis and embolism. Probably there are numerous reasons which account for this fact, some of which may be a shorter period of confinement in bed, distance of operative field from the usual sites in which thrombosis occurs, lesser degree of trauma to large veins, less interference with respiratory tract during the postoperative period, less effect on postoperative rate of venous flow, and so forth. The fact that the extent of the surgical procedure is not the only factor of importance is illustrated by the observation that thrombosis and embolism after radical amputation of the breast, which certainly is an extensive surgical procedure, occur less

From the Division of Surgery, and the Division of Medicine, Mayo Clinic.

TABLE I*.—RELATIVE INCIDENCE OF THROMBOPHLEBITIS AND PULMONARY EMBOLISM AFTER VARIOUS TYPES OF SURGICAL PROCEDURES

Operation on	Cases	Clinical diagnosis Thrombophlebitis		Pulmonary embolism			
				Total		Fatal	
		Number	Per cent	Number	Per cent	Number	Per cent
Head and neck	50,844	19	0.04	32	0.06	14	0.03
Extremities and trunk	18,839	19	0.10	22	0.12	14	0.07
Thorax	1,779	5	0.28	9	0.51	2	0.11
Radical removal, breast	2,919	26	0.89	17	0.58	5	0.17
Exploratory laparotomy for inoperable malignancy	2,427	20	0.82	29	1.19	17	0.70
Resection, stomach (mostly carcinoma)	2,246	33	1.47	31	1.38	13	0.58
Other gastric operations (mostly benign)	10,278	112	1.09	112	1.09	35	0.34
Gall bladder and ducts	13,103	143	1.09	119	0.91	47	0.36
Abdominal hysterectomy	5,730	163	2.84	87	1.52	42	0.73
Splenectomy	391	10	2.56	13	3.32	3	0.77
Appendectomy (appendix unruptured)	7,975	38	0.48	36	0.45	6	0.08
Appendectomy (appendix ruptured)	835	7	0.84	12	1.44	3	0.36
Unilateral femoral or inguinal hernia	3,852	28	0.73	29	0.75	14	0.36
Bilateral femoral or inguinal hernia	661	13	1.97	10	1.51	4	0.61
Resection, intestine	2,571	25	0.97	62	2.41	16	0.62

*Partial tabulation of entire group of 172,888 cases reviewed.

often than after many abdominal operations of lesser magnitude.

In some way, unexplained at present, the presence of cancer seems to predispose to thrombosis and embolism. Operations performed on the stomach for malignant conditions are followed by a higher incidence of thrombosis and embolism than are gastric procedures performed for benign lesions. The incidence of fatal pulmonary embolism after exploration alone for malignancy is unusually high and is virtually the same as that for abdominal hysterectomy or splenectomy, the other procedures which most often are followed by fatal pulmonary embolism, it is possible that the poor general condition of the patient, anemia, loss of weight and strength, inanition and other general changes associated with inoperable cancer in this regard are as important as, or even more so than, the actual malignant lesion itself. Thrombosis or embolism may develop among patients with cancer, even though no surgical procedure has been performed.

The relative frequency of phlebitis and embolism after pelvic operations has been mentioned by many authors. Our experience has been similar. Thus, it is seen that the incidence of embolism and thrombophlebitis is much higher after abdominal hysterectomy than after operations on the gall bladder and bile ducts, both types of operations being done for the most part for benign conditions. The relative magnitude of these procedures is very similar, so it becomes apparent again that the site of operation must be a factor of some importance. In pelvic operations there is of course a greater chance of traumatizing veins, both large and small, and perhaps of retarding venous circulation at least temporarily by pressure on the iliac veins. Likewise, more veins are ligated in the performance of hysterectomy than in an ordinary operation for disease of the gall bladder.

Splenectomy is followed by the highest incidence of embolism of any surgical procedure (Table I). This is not surprising, however, since when splenectomy is performed the surgeon deals directly with the hematopoietic system, and the operation generally is performed in the presence of some type of blood dyscrasia, both of which factors might well

TABLE II.—INCIDENCE OF POSTOPERATIVE THROMBOSIS AND EMBOLISM IN RELATION TO AGE IN ABDOMINAL HYSTERECTOMY

Age, years	Operations	Thrombosis or embolism	
		Number	Per cent
Less than 20	10	0	—
20–29	168	3	1.8
30–39	1449	42	2.9
40–49	2870	126	4.4
50–59	975	48	4.9
60+	258	11	4.3
Total	5730	230	4.0

TABLE III.—INCIDENCE OF THROMBOSIS AND EMBOLISM AFTER ABDOMINAL HYSTERECTOMY

Complicating features	Cases	Thrombosis and embolism	
		Number	Per cent
None	3,184	62	1.9
Any of following complications	2,546	168	6.6
Cardiac disease*	237	17	7.2
Diseases of peripheral veins*	443	25	5.6
Disease of blood*	1,241	116	9.3
Carcinoma*	623	29	4.7
Severe infection*	678	39	5.8
All cases	5,730	230	4.0

*Sum of the complicating features will not equal the total number of patients having predisposing conditions because some patients had more than one predisposing condition.

contribute to thrombosis. Certain types of blood dyscrasia, of course, have a notoriously high incidence of associated thrombosis.

That infection has some relationship to the postoperative development of thrombosis and embolism is suggested by the fact that both thrombosis and embolism occur with much greater frequency after operation for a ruptured appendix than after removal of an unruptured appendix. Of course, it might be argued that the generally poor condition of the patient in the presence of a ruptured appendix is the main factor, rather than infection. The importance of infection, however, is verified in other ways. Magnitude of the operation, if other factors such as location of the operation, type of lesion, condition of the patient, and so forth are kept constant, appears to be of some significance. Thus, thrombosis and embolism occur approximately twice as often after bilateral inguinal herniorrhaphy as after repair of unilateral hernia.

Other factors influencing the incidence of thromboembolic phenomena. It has been observed that the incidence of postoperative thrombophlebitis is higher in women than in men, the ratio being approximately 3:2(2). In contrast, the occurrence of pulmonary embolism, both fatal and nonfatal, is higher in men than in women. Why thrombosis should occur more often in women and embolism more often in men is not clear. It cannot be explained on the basis of the difference in surgical procedures performed on the two sexes. As is well known, thrombosis and embolism occur relatively seldom in the young patient. This general impression is substantiated by our findings as shown in Table II. It is noted that in a consecutive series of cases in which abdominal hysterectomy was performed, for example, the incidence of thromboembolic phenomena among patients more than 40 years of age was definitely greater than it was among those less than 40 years of age. As age increased beyond this point, there seemed to be no corresponding increase in the incidence of thrombosis or embolism, since the incidence remained between 4 and 5 per cent for all persons more than 40 years old.

In order to evaluate the possible importance of certain definite complicating features predisposing to thrombosis and embolism, it is necessary to consider a single surgical procedure. For this purpose abdominal hysterectomy was chosen (Table III). As seen in this table, there are certain factors which definitely predispose to postoperative thrombosis and embolism. Any disease of the veins, such as varicose veins or residual effects of old thrombophlebitis, increase the chance of development of some form of thromboembolic episode after operation. Likewise, cardiac disease such as chronic valvular lesions, hypertensive heart disease, auricular fibrillation or coronary disease, predisposes to thrombosis or embolism after operation. In fact, it has been observed by Belt of patients who succumb to various medical conditions, with evidence at

TABLE IV.—RELATIONSHIP OF VENOUS THROMBOSIS OR THROMBOPHLEBITIS TO EMBOLISM

Evidence found	Embolism			
	Total		Fatal	
	Number	Per cent	Number	Per cent
Without clinical evidence or evidence at necropsy of venous thrombosis or thrombophlebitis	405	45.2	135	39.4
Evidence at necropsy but no clinical evidence of venous thrombosis or thrombophlebitis	265	29.5	157	45.8
Clinical evidence alone of venous thrombosis or thrombophlebitis	227	25.3	51	14.9
Total	897	100	343	100

postmortem examination of thrombosis or embolism, that cardiac disease is more prevalent than any other condition. With the additional factor of operation, such as hysterectomy, it is to be expected that the occurrence of thrombotic or embolic phenomena would be relatively common in this group of patients. Patients who undergo hysterectomy in the presence of diseases of the blood, such as anemia, polycythemia vera, leucemia, and thrombocytopenic purpura, have thrombosis or embolism more often than do any other group of patients in which hysterectomy is performed. Many of these conditions, of course, even in the absence of operation, predispose to thrombosis, and the high incidence of the latter in the presence of these conditions seems to emphasize the possible importance of hematological changes of subclinical degree in the average surgical patient in whom thrombosis or embolism occurs. As mentioned previously, malignant lesions and severe infection also make such complications more likely. In addition, it has been observed that obesity is a predisposing factor (28). Other factors which have been considered, but which were not found to be significant, were the type of anesthesia employed and the season of the year.

Time of occurrence postoperatively. It is well known that thrombophlebitis occurs most often during the postoperative period before the patient leaves the hospital. In a recent study of 938 cases in which the clinical diagnosis was thrombophlebitis, it was noted that in approximately one-half of the cases the diagnosis had been made between the 9th and the 14th postoperative days (3). In approximately half of the remaining cases the condition occurred prior to this time, and in an equal number it was recognized later. It is true of course that in some cases thrombosis may have been present for a variable length of time before it was recognized clinically. In approximately 10 per cent of these 938 cases there was more than one distinct episode of phlebitis. In two-thirds of the cases in which multiple episodes occurred the interval between the first and last episode (in case more than two occurred) was 1 to 9 days.

A roughly comparable time of occurrence during the postoperative period was noted in the 897 cases of pulmonary embolism, both fatal and nonfatal. In approximately a fourth of all cases of embolism the condition occurred prior to the 7th postoperative day, in a half, from the 7th to the 14th day inclusive, and in the remainder, after 2 weeks.

Relationship between thrombosis and embolism. That a relationship between venous thrombosis or thrombophlebitis and embolism exists in many cases seems certain; yet, in other cases there is no recognizable thrombotic phenomenon prior to the sudden appearance of embolism (Table IV). In all the 897 cases of embolism there was no clinical evidence or evidence at necropsy, in patients examined in this manner, of venous thrombosis or thrombophlebitis in approximately a half of the cases, 45.2 per cent (4). In only a fourth of the cases of embolism was there clinical evidence of venous thrombosis or thrombophlebitis. Of the group in which fatal embolism occurred, these conditions were detected clinically in only 14.9 per cent of cases (Table IV). The case in which sudden fatal pulmonary embolism occurs with no antecedent warning is only too well known to all. It seems likely that venous thrombosis may develop and all of the thrombus may become dislodged to form an embolus within so short a period that subsequently, even at necropsy, no change can be detected in the vein from which it arose. Similarly, venous thrombosis, because of lack of reaction in the vein, may cause

symptoms inadequate to be recognized clinically. Thrombosis which occurs in a vein and remains for any appreciable length of time probably results in adherence of the thrombus to the wall of the vein, so that the formation of an embolus from this source is unlikely. However, it is possible that such a thrombus may suddenly grow proximally, and thereby give rise to a loosely attached clot which might become dislodged and form the source for a pulmonary embolus. This same mechanism probably explains why pulmonary embolism does not occur more frequently after definite thrombophlebitis has been recognized clinically because the thrombus has become adherent. This does not mean that a patient who has thrombophlebitis in one leg, for example, may not subsequently have venous thrombosis in the other leg which may constitute the source for a pulmonary embolus. It was observed that pulmonary embolism occurred in 24.2 per cent of 938 cases in which the clinical diagnosis was thrombophlebitis. In only 4.4 per cent of cases did the embolism appear later than 6 days after the diagnosis of thrombophlebitis had been made.

Prevention of thrombosis and embolism. Much study and effort has been directed toward the prevention of postoperative thrombosis and embolism, but as yet no completely satisfactory prophylactic measure has been evolved. Many different forms of treatment, medication, physical measures, postoperative routines, and so forth have been suggested, but none has proved to be the ideal solution to the problem. Prophylactic treatment has not been effective for various reasons, one of which is an incomplete appreciation of the etiology of venous thrombosis or thrombophlebitis and embolism. There appear to be three main etiological possibilities for postoperative venous thrombosis: namely, (1) decrease in the rate of venous blood flow with resultant stasis, (2) trauma or other type of change in the wall of the vein, and (3) some abnormality in the blood itself. It seems likely that the etiology of thrombosis is not represented by a single constant factor, but that often more than one factor is present. In some cases certain factors may be of paramount importance and others of minimal significance, whereas in other cases the reverse may be true. It has been demonstrated that the rate of venous blood flow is retarded during the postoperative period (27) and that the time of greatest slowing occurs during the interval in which thrombosis and embolism develop most commonly. Almost all investigators agree that venous stasis may be a factor of considerable importance in many cases of thrombosis. In addition, it seems possible that certain abnormal clotting factors which as yet have escaped clinical recognition may be active in certain cases. Local trauma to large veins is associated with the possibility of subsequent thrombosis in the mind of every surgeon and, obviously, is avoided as much as possible.

One of the serious difficulties in the preventive treatment of thrombosis and embolism is our inability to determine before operation in which patient, if he is not treated, thrombosis or embolism will develop after operation. If this could be accomplished the problem of prophylaxis virtually would be solved at present. The fact that such knowledge cannot at present be gained before operation means that any prophylactic measures which are to be successful uniformly must be employed in all surgical cases. This in turn necessitates that any therapy instituted for this purpose be without hazard, of reasonable cost, readily carried out, highly effective, and as foolproof as possible. No such treatment exists today, although certain work that now is in progress may bring about a definite advance in this regard. At the present time measures designed to increase the rate of venous blood flow are widely used. These consist of use of the Trendelenburg position, routine exercise of the legs, massage of the legs, application of heat to and elevation of the legs, production of deep respiration by use of carbon dioxide in one of several forms, early postoperative physical activity, medication of one type or another, and various forms of treatment of recognizable venous thrombosis and thrombophlebitis in an effort to prevent extension or new thrombosis and therefore a possible embolus. Experimentally, thyroid extract increases the rate of venous blood flow. As it is employed clinically, however, this may not

always be the case, since the physiological effects of a given dose vary widely in different cases. Of the newer forms of prophylactic treatment, heparin has been most effective in the group of cases in which it has been employed for this purpose. Crafoord (10) reported that among 325 patients who underwent major surgical procedures and had received prophylactic heparin therapy during the years 1937 to 1940, thromboembolic complications developed in only 3. This experience is in contrast to that obtained in a group of 302 similar patients operated on during the same years to whom heparin was not administered and among whom thrombo-embolic phenomena of one type or another developed in 17.5 per cent. Murray and Best (20, 22, 23) have reported similar experiences. Unfortunately, in its present form, heparin is not suitable for routine postoperative use. Recently, Welch and Faxon have emphasized the value of extraction of venous clots and subsequent venous ligation in the prevention of emboli after the development of venous thrombosis or thrombophlebitis.

Administration of heparin. Although heparin was first isolated by McLean in 1916 and later named by Howell and Holt and first employed for the prevention of experimental thrombosis and embolism by Mason in 1924, only during recent years has its clinical use become feasible with isolation of a purified form of heparin which can be administered to patients without the production of toxic manifestations. Charles and Scott, working with Best in Toronto, and Jorpes (17) working in Sweden, and Schmitz and Fischer in Germany, all working independently, produced such a form of heparin. With this new nontoxic heparin available, numerous reports of its experimental and clinical use have appeared, especially from Murray, Best and their associates in Toronto (21, 22, 24), and also Crafoord (11, 12), other Scandinavian workers, and others (5, 9, 13, 16, 17, 30).

At the present time there are two general methods for the administration of heparin; the method employed largely by the Scandinavians of giving repeated single injections and that used mostly in this country of continuous intravenous administration of it in physiological solution of sodium chloride or in a 5 per cent solution of glucose. When divided doses are employed, 4 doses are given during the course of 24 hours, 3 of 50 milligrams each during the day, and one of 100 milligrams at bedtime, or, occasionally, 3 of 75 milligrams each during the day and one of 125 milligrams in the evening. These are the doses recommended by Crafoord for the Scandinavian product, and he reported most satisfactory results. We have had no experience with this form of treatment, although we appreciate that when it is desirable to avoid the intravenous use of fluids this form of administration might be most useful. Work in progress at the present time may develop a method whereby a uniform effect can be exerted by heparin for a period of 24 hours or longer, by a single injection.

When heparin is given by means of continued intravenous injection, the physician should endeavor to maintain the venous coagulation time of the blood at a value of from 15 to 20 minutes. There is considerable variation in the amount of heparin necessary to accomplish this purpose in different individuals and also perhaps at different times in the same patient. A starting dosage of approximately 20 milligrams per hour of the Toronto product or an equivalent amount of one of the several available commercial products of heparin usually is satisfactory. This dosage then must be regulated according to requirements of the individual patient. It is essential, when heparin is administered by means of continuous intravenous injection, that the rate of flow be watched closely and the coagulation time of the blood be determined as often as necessary (2 to 6 times daily), so that it may be certain that the rate of flow and coagulation time remain within the desired limits. When once started, the administration of heparin should be continued for a minimum of 7 to 10 days or longer if conditions indicate. Repeated periods of administration may be necessary in a few cases. Prompt return of the coagulation time to normal within a matter of several hours follows discontinuance of the administration of heparin. This is greatly hastened by the administration of proamine sulfate, which will

cause return of the coagulation time to normal within a few minutes (17). It is advisable to continue the use of heparin until the patient has been out of bed for several days. The advantage of the continuous administration of heparin as compared to repeated individual injections resides in the more constant prolongation of coagulation time which it affords, as opposed to the situation represented by a curve of coagulation time which constantly ascends and declines, resulting from repeated single injections. The obvious advantage of the latter method is its simplicity, but some patients may object more to repeated intravenous injections than to continuous intravenous infusion. Current work may evolve a more satisfactory form of administration than either of the two now commonly employed.

Indications for the use of heparin. Granted that heparin is not to be administered to every surgical patient, to what group of patients should it be administered? Inasmuch as we cannot prophesy before operation which patient will be afflicted by thrombosis or embolism, we have no accurate indication for the use of heparin with the hope of preventing all postoperative thromboembolic phenomena. It would appear reasonable to employ it for any person who, because of previous phlebitic or embolic phenomena or other reasons, is expected to experience further difficulties in this regard. In a few such cases we have employed heparin with completely satisfactory results. Otherwise, it can be said that the group of patients in which embolism is most likely to occur is that group in which one episode of nonfatal embolism already has occurred. It is this group to which we have largely limited the administration of heparin.

Some idea of the possible number of patients who might be benefited by the administration of heparin (that is, patients who already have manifested some evidence of embolism) is shown in Table V. It is noted that of the entire group of 897 patients who had embolism, approximately a half (52.5 per cent) had only a single episode, which was nonfatal. Approximately a fourth (24.4 per cent) had a single episode which was fatal. The remaining fourth (23.0 per cent) had multiple episodes, some of which ended fatally and some of which did not. If only those patients who had fatal pulmonary embolism are considered (a total of 343 cases), it is seen that 124 or 36.2 per cent had multiple episodes of embolism. Thus, on the basis of this table it would appear that approximately one of three people who now die of postoperative pulmonary embolism could be saved if heparin was administered properly on the first indication of an embolic phenomenon and if the procedure proved to be 100 per cent effective as a prophylactic measure against further embolism. Such perfection could hardly be anticipated, but it is mentioned to show what might be accomplished under the most favorable circumstances. If all the patients who had embolism and survived its immediate effects are considered, it is seen that 33 per cent had one episode or more subsequently and that 18.3 per cent died of subsequent embolism. Of the group of patients who had multiple embolisms, 59.9 per cent died of embolus. An additional number of patients likewise could be spared the morbidity and prolonged hospitalization which so frequently are associated with recurring pulmonary emboli which are nonfatal. Furthermore, of the 938 patients who had clinical thrombophlebitis, 10.1 per cent had one or more subsequent episodes of thrombophlebitis; 15 per cent subsequently had embolism and 5.4 per cent had fatal embolism. It is probable that these subsequent episodes could be prevented by the use of heparin.

TABLE V.—NUMBER OF EPISODES COMPARED TO FATALITY, POSTOPERATIVE PULMONARY EMBOLISM

Episodes and outcome	Cases	Per cent
One only; nonfatal	471	52.5
One only; fatal	219	24.4
Multiple; nonfatal	83	9.2
Multiple; fatal	124	13.8
	897	100

Clinical experience with heparin. Clinical experience with heparin for patients who had experienced nonfatal pulmonary embolism has been most gratifying. Heparin has been administered to 63 such patients and only 2 of these, or 3.2 per cent, subsequently succumbed

to another episode of embolism. Both of these deaths occurred early in our experience and heparin had been administered for only 2 days, a period which we now know was entirely inadequate. Both deaths occurred after the administration of heparin had been discontinued and the coagulation time had returned to normal. Even so, this figure of 3.2 per cent of embolic deaths due to embolism among patients treated with heparin compares most favorably with a death rate from embolism of 18.3 per cent in members of the untreated group of patients, who had anything other than an originally fatal single embolus.

In addition to the prevention of death from subsequent emboli, it has been observed that among patients receiving heparin amelioration of clinical symptoms of emboli, such as pain in the thorax, elevation of temperature, and increase in pulse rate, frequently occurs more rapidly than might be expected otherwise. Not only will the proper use of heparin in most cases prevent subsequent fatal emboli, but it will also obviate further nonfatal emboli in most cases. There have been a few instances in our experience in which further nonfatal emboli occurred some time after discontinuance of the administration of heparin, and in some cases heparin has been given as often as three times, with an interval of perhaps a week or more between each two periods of treatment. Heparin has been employed as a prophylactic measure with completely satisfactory results for a few patients who, because of previous phlebitis or embolic phenomena, were considered to be especially likely to experience complications of this type after any surgical procedure. In none of these cases did phlebitis or embolism develop. Almost never has there been evidence of further embolic phenomena during the administration of heparin, but in 4 cases a sudden increase in thoracic pain during the administration of heparin has suggested such a possibility.

Unfortunately, heparin offers little for the patient who has sudden massive pulmonary embolism which in the ordinary course of events proves to be fatal in a matter of minutes or several hours. Likewise, it will not prevent the pulmonary reaction which is to be expected in association with the initial embolus. If the embolus has been a large one, subsequent evidence of pneumonia may develop and in some cases prove to be a serious complication. Bleeding, which ordinarily would not be expected, has occurred in a few cases during the administration of heparin, but in no case has this proved to be a serious factor. In 2 cases there was some bleeding into the wound when the administration of heparin was started soon after operation and when the coagulation time was permitted to become unduly prolonged. In 4 cases hematuria occurred. In all instances bleeding promptly ceased after the administration of heparin had been discontinued. It is apparent that heparin does not offer the ideal solution to the problem of postoperative embolism, although it is possible that certain improvements in its use may enhance its value in the future. Recently, another anticoagulant, 3,3′-methylene-bis-(4-hydroxycoumarin), has been suggested, and work with this product is now in progress (7). It is possible that this may largely supplant heparin as an anticoagulant in the prevention and treatment of thrombophlebitis and embolism.

Our experience with the use of heparin in the treatment of thrombophlebitis has been more limited and less definite than in embolism. There is so much variation in the clinical course of thrombophlebitis, depending on its location, site, extent of infection present and general condition of the patient, that definite criteria in a group of control cases are not readily obtained. It is our impression, however, that heparin will prevent further growth of a thrombus and in this manner prevent aggravation of the condition. Furthermore, it prevents other thrombi from developing during the course of its administration. In addition to the suggestions of the use of heparin and the conventional treatment of immobilization, elevation, and heat, other suggestions have been made during recent years for the treatment of thrombophlebitis, and favorable results have been reported. These include paravertebral injection, as it has been stressed by Ochsner and DeBakey, and venous ligation, as suggested by Welch and Faxon.

SUMMARY

Pulmonary embolism in our experience is responsible for approximately 6 per cent of deaths which occur after major surgical procedures. A number of factors influence the likelihood that embolus or thrombosis will follow any operation, and these include site of the operation, magnitude of the procedure, presence of infection or malignancy, diseases of the blood or cardiovascular system, obesity, age, and sex. The majority of all thromboembolic phenomena occur within the first 2 weeks after operation. Approximately 1 in 4 cases of pulmonary embolism is associated with clinical evidence of thrombophlebitis, and similarly, approximately 1 in 4 cases of thrombophlebitis is associated with evidence of embolism. Of all patients who experience pulmonary emboli, approximately one-half have a single nonfatal embolus; one-quarter have a single fatal embolus, and the one-quarter remaining have multiple emboli which in approximately 60 per cent of cases are followed, finally, by fatal embolism. Proper use of heparin in all cases in which evidence of nonfatal pulmonary embolism is available should prevent about one-third of the deaths which now occur from postoperative pulmonary embolism.

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CYTOLOGICAL FACTORS IN PERITONITIS AND PERITONEAL IMMUNITY

H. B. MORTON, M.D., M.S., Lincoln, Nebraska

PERITONITIS continues to offer the greatest hazard as a complication of intra-abdominal surgery and intra-abdominal inflammatory processes. This fact no doubt has provided the incentive for the vast amount of experimental and clinical investigation which has been carried out in an attempt to combat this common pathological process.

Reports of experimental work on peritoneal immunity extend back to the work of Issaeff in 1894, but it is only since about 1927 that extensive experimental and clinical studies have been made. Goldblatt and Steinberg found that small repeated intraperitoneal injections of a culture of Bacillus coli would produce immunity against a subsequent lethal intraperitoneal injection of the same organism. Herrmann produced similar findings with a killed mixed culture of the Streptococcus viridans and the colon bacillus. Both of these experimental results have found clinical application (8, 13, 14).

These findings were highly suggestive that this locally induced immunity was specific in character. In an attempt to produce peritoneal immunity experimentally with specific bacterial filtrates (antivirus) it was discovered that nonspecific innocuous substances, as glucose solution, would work equally as well. (7). It was also noted that the element of time was a factor in the development of an adequate defense against definitely lethal intraperitoneal inoculations. This local peritoneal immunity was dependent upon, or associated with, the presence of an increased number of macrophage cells. Suggestive evidence was presented that these cells originate from the endothelial cells of the omentum.

Since my report of this work, other investigators have made similar findings, both clinically and experimentally. Several writers have expressed the belief that local peritoneal immunity is nonspecific in type regardless of the activating agent, and some have stated that nonspecific substances work equally as well if not better in producing such an immunity. In comparing mixed vaccine (Bargen), sodium ricinoleate and amniotic fluid concentrate, Seeley, Higgins, and Mann found the greatest response by the mononuclear cells was produced by sodium ricinoleate, about 72 hours after its peritoneal injection, and the next greatest response was by amniotic fluid concentrate after 168 hours. Corwin found the true quantitative cellular response to the intraperitoneal injection of sodium ricinoleate to be nearly twice that to Bargen's vaccine (intraperitoneal). He concluded that any of a large number of so called specific or nonspecific substances should prove equally effective in producing a local peritoneal immunity, that 1 to 3 days before operation seemed the optimum time for the injection, and that the induced immunity was dependent upon the presence of histiocytes.

Rixford found at varying intervals after the intraperitoneal injection of vaccine (Bargen) in man that the total cell count and the percentage of polymorphonuclear cells were greatly increased, but that the smoothness of the convalescence was proportional to the total number of histiocytes present.

With the use of the sulfonamide group of drugs in the local treatment of infection, application has been made to the peritoneal cavity. Throckmorton found experimentally that the cellular responses elicited by these various compounds were qualitatively those of nonspecific peritoneal irritation. The quantitative differences seemed due to variation in solubility and irritation rather than specific cellular stimulation. Of the various drugs studied, sulfathiazole seemed best suited as a stimulant of peritoneal defense. In an excellent detailed discussion of the literature and his own experimental and clinical findings on the various methods of preventing and

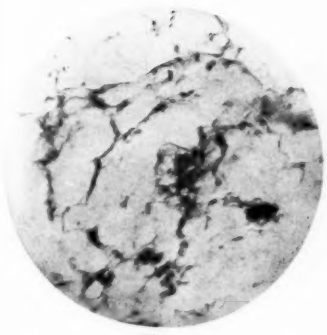

Fig. 1.

Fig. 1. Photomicrograph of a section of normal omentum (low power).

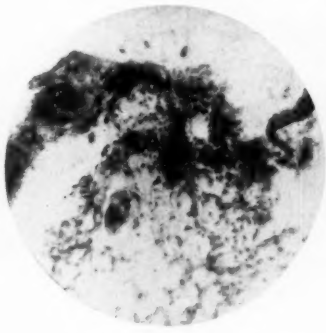

Fig. 2.

Fig. 2. Photomicrograph of a section of omentum from patient 48 hours after the intraperitoneal injection of amfetin (low power).

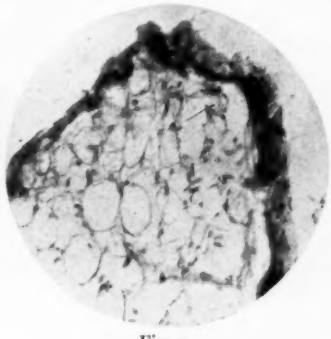

Fig. 3.

Fig. 3. Photomicrograph of section of the omentum from the same patient as that shown in Figure 2, but removed 3 weeks later. In this specimen is observed normal cytology except for the presence of fibroblasts at the margin (low power).

treating peritonitis, Rea states that his results obtained with the sulfonamides were impressive but questionably better than those obtained with other substances when used prophylactically.

Surgeons have recognized for years the importance played by the great omentum in combatting intra-abdominal inflammatory processes. That the omentum will migrate to an area of inflammation and attempt to keep it localized by walling it off is common knowledge. The other defensive responses on the part of the omentum are not generally known. Experimentally it has been shown that there is a definite cellular response in the omentum to intra-abdominal invasion by bacteria (7).

It is my purpose at this time to describe the response of the omental tissue of man to intraperitoneal infection or irritation. Recently I have studied stained sections of omenta from patients who have had preoperative intraperitoneal injections and from patients in whom acute or subacute intra-abdominal inflammatory reaction was found at operation. In this study the intraperitoneal injections were made with amniotic fluid concentrate (amfetin) 48 hours prior to colon surgery. The cases of intra-abdominal inflammatory disease were divided between acute appendicitis, subacute cholecystitis, subacute salpingitis, ruptured ectopic pregnancy, and evisceration of abdominal contents.

These omenta on gross inspection vary in color from slight pinkish tint to light red color and are a common finding in an acute or subacute abdominal condition. On microscopic section these omenta show dilatation and engorgement of the capillaries commensurate with the amount of inflammatory reaction as evidenced by color. Around the capillaries and in the connective tissue meshwork are varying numbers and proportions of polymorphonuclear leucocytes and mononuclear cells. This number and proportion vary with the severity and duration of the intraperitoneal irritation. In the cases in which the infection or irritation has been of short duration, the predominant cell is found to be the polymorphonuclear neutrophile. Where the process is of longer duration, there is a shift in favor of the monocytes. No attempt has been made to classify these monocytes but, following the usage of Witts, the term macrophage might well be used to include all cells which have been variously designated as histiocyte, clasmatocyte, etc.

All writers on the subject of peritoneal immunity seem to agree on the point that this defense is dependent upon a local leucocytosis (12), but opinion seems divided as to the relative importance of the polymorphonuclear cell and the mononuclear cell in the defense mechanism. A fairly constant finding in favor of the monocyte as the more impor-

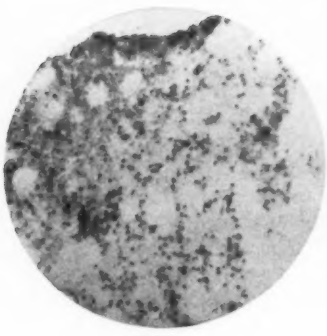

Fig. 4.

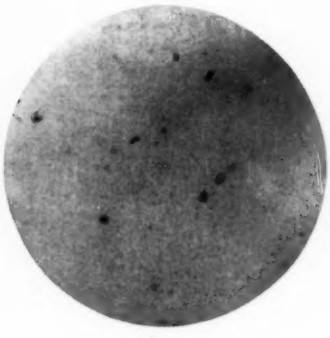

Fig. 5.

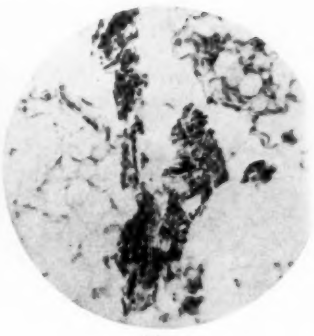

Fig. 6.

Fig. 4. Photomicrograph of section of omentum in acute appendicitis, early, showing moderate diffuse infiltration of cells, mostly polymorphonuclear leucocytes (low power).

Fig. 5. Photomicrograph of smear of peritoneal fluid in case of appendicitis about 24 hours after onset, showing occasional polymorphonuclear leucocyte (low power).

Fig. 6. Photomicrograph of section of omentum from same case shown in Figure 5, showing heavy concentration of cells around the capillaries; about 90 per cent of which are monocytes (low power).

tant cell in peritoneal defense is the corresponding interval of time required for establishment of immunity and mobilization of the macrophage cells. This latter type of cell has also been shown to possess greater phagocytic power. It has also been shown experimentally that the presence of enormous numbers of polymorphonuclear leucocytes alone will not successfully combat extensive intraperitoneal infection (7).

Intraperitoneal immunity is always a variable quantity, and its adequacy in protecting the organism against the invasion of pathogenic organisms will be determined in any given case by balancing the strength of the local defense mechanism against the magnitude of the invading infection. Bargen states that his method of preoperative intraperitoneal vaccination will not always prevent peritonitis where gross soiling occurs but it does help to mobilize the defensive forces. Even when the defensive forces respond to an appreciable extent, they may still prove inadequate to overcome a massive infection.

The mode of entry of the macrophage cells into the peritoneal cavity offers an interesting speculative study. In the omentum they are seen grouped around and in very close proximity to the capillaries. This same observation has been made in sections of peritoneum from immunized animals (7). In clinical cases of acute suppurative appendicitis, it is possible to find a perivascular grouping of cells in the omentum before they appear in increased numbers in the peritoneal fluid as will be shown later. The work of Higgins and Bain suggests the possibility of lymphatics or similar channels adjacent to the capillaries of the omentum. Since histiocytes are seen first to increase in these areas, it is quite possible that they have their origin from these perivascular areas, the cells of which may belong to the reticuloendothelial system.

The great omentum from an abdomen free of infection or irritation is quite acellular and is composed of loose areolar meshwork containing blood vessels and adipose tissue (Fig. 1). Forty-eight hours after the intraperitoneal injection of 50 cubic centimeters of amniotic fluid concentrate, there is a definite engorgement of the capillaries of the omentum and a marked increase in the cellular content, a large percentage of which is monocytic (Fig. 2). The omentum of this same patient studied 3 weeks later without preoperative injection again appeared normal except for fibroblastic changes at the margin (Fig. 3).

The developmental cytological changes associated with developing intraperitoneal irritation or infection can best be followed in cases of appendicitis in different stages or periods of development. In the earliest stages of acute appendicitis, there may be no detectable increase in intraperitoneal fluid and

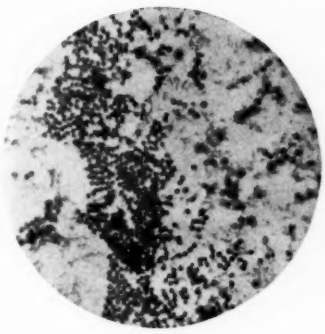

Fig. 7.

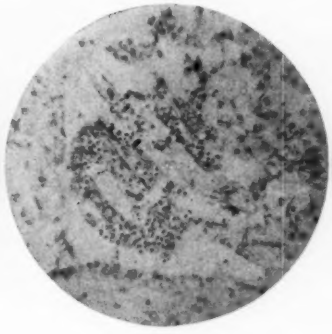

Fig. 8.

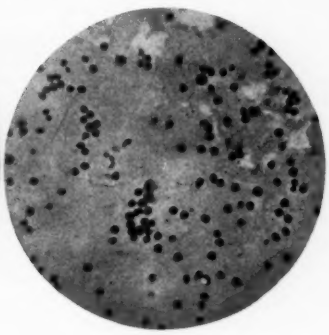

Fig. 9.

Fig. 7. Photomicrograph of smear of peritoneal fluid in a case of peritonitis 36 hours after onset. Appendix gangrenous but not perforated. Heavy concentration of cells; a large percentage of which are monocytes (low power).

Fig. 8. Photomicrograph of section of the omentum from a case of ruptured appendix. This specimen shows a moderate infiltration of cells, all of which are monocytes (low power).

Fig. 9. Photomicrograph of smear of peritoneal fluid from same case as shown in Figure 8, shows moderate concentration of cells, the majority of which are polymorphonuclear leucocytes (high power).

without increase in cellular content, but there may be an increase in the cellular content of the omentum. At this early stage a large percentage of the cells are found to be polymorphonuclear neutrophiles (Fig. 4). In a more acute involvement of the appendix about 24 hours after the onset of symptoms, a definite increase in thin amber peritoneal fluid has been found which contained only an occasional polymorphonuclear leucocyte and no monocytes (Fig. 5). The omentum of this same case showed a heavy concentration of cells, about 90 per cent of which were monocytes, arranged mostly around the capillaries (Fig. 6). When a case has become more advanced after a period of about 36 hours but before perforation has occurred, the cellular pattern of the omentum may contain a heavier infiltration of monocytes, but at this stage of development the peritoneal fluid will usually contain a heavy infiltration of cells, a large percentage of which may be monocytes (Fig. 7).

This apparently is the defense mechanism which nature sends out in advance of an impending bacterial invasion. For we have similar findings in a case of a ruptured appendix with generalized peritonitis about 40 hours after the onset of symptoms. A moderate infiltration of cells, all of which were monocytes was seen in the omentum (Fig. 8). In this case a majority of the moderate number of cells in the peritoneal fluid was found to be polymorphonuclear neutrophiles (Fig. 9). No bacteria were found in the fluid (Fig. 10). The clinical course was stormy but satisfactory with no doubt a gradual increase in the number and percentage of the macrophage cells. These last 2 cases demonstrate the individual variation in the development of a local peritoneal immunity and that there is a definite quantitative factor in its production.

Evaluation

There are very definite clinical deductions which can now be made from these findings. The cellular defense mechanism is apparently

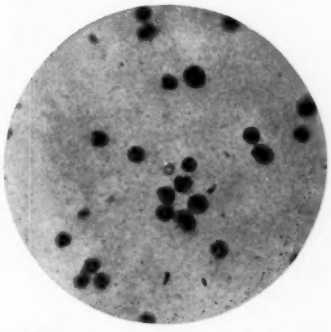

Fig. 10. Photomicrograph of same smear as shown in Figure 9 (oil immersion) showing detail of a group of macrophage cells.

set into motion by any irritation or foreign substance within the peritoneal cavity. A markedly inflamed intra-abdominal organ may be the exciting factor in calling out the defense forces against any possible subsequent infection. In generalized peritonitis, the diffuse presence of the infection and inflammatory exudate is as great a stimulus to the defense mechanism as any other foreign agent would be. For this reason there is no scientific background for the use of various substances intraperitoneally in the presence of generalized peritonitis for the purpose of increasing peritoneal defense. This is in conformity with the clinical observations of Rea. He has noted, however, very definite clinical value in the use of sulfonamides intraperitoneally in what he terms the preperitonitis phase of a local intraperitoneal infection or soiling.

On the basis of our present knowledge of peritoneal immunity, our treatment must at least in a sense be prophylactic. The use of vaccines, sulfonamides, and other substances at the time of local soiling or contamination has a rational basis, as these substances may set up a defense reaction before the infection has time to increase and spread. It is this increase in defense mechanism ahead of the infection which can be considered of real value.

It must be admitted that the ideal substance or method for inducing peritoneal immunity has not been found. It has been described as one which is innocuous, free from side reactions, has a short immunizing period and produces immunity similar to that developed by the normal peritoneal cavity against infection (9). From an analysis of the presented facts it is apparent that all of these can be fulfilled except the element of time which is involved in producing an immunity which is adequate against an infection of any magnitude.

It has been possible to produce such an immunity in animals, but it requires 2 to 4 days' time and the possibility of repeated injections (7).

This is possible in preoperative preparation only. To combat a spreading infection from soiling at operation or from a perforated viscus, the best substance at the present time seems to be sulfathiazole. It is probably bacteriostatic in addition to being an excitant of local peritoneal defense and is absorbed quite slowly. The ideal substance in treating peritonitis, either generalized or local, might well be a rapidly acting germicide with low irritability, great diffusibility, slow rate of absorption, and be unaltered by exudate or moderate dilution. Such a substance would also provide adequate stimulation to the cellular defense mechanism.

In cases of intraperitoneal infection with varying amounts of increased intraperitoneal fluid, it is quite general practice for surgeons to aspirate this fluid. From the presented studies of this fluid, the rationale of this procedure as a routine practice might well be questioned. It might be suggested that a study of this fluid by means of stained smears at operation would yield information which would influence one in the proper disposition of this fluid and the proper management of the peritoneal cavity. Soon after the perforation of a heavily infected viscus as the colon, if the peritoneal fluid showed a low cell count and high bacterial count, aspiration of any fluid or foreign material and irrigation of the peritoneal cavity, either locally or generally as indicated, might be a valuable procedure. On the other hand if a smear showed the balance of power to be in favor of the cellular elements, then harm would most certainly result from the generally condemned procedure of irrigating the peritoneal cavity or from aspirating the fluid present.

SUMMARY

1. Previous studies have shown that peritoneal immunity is dependent upon, or at least associated with, the presence of large mononuclear (macrophage) cells in the peritoneal fluid.

2. Findings are now presented which show that these cells also appear in the omentum of patients with peritonitis or who are immunized against intraperitoneal infection.

3. Evidence is presented to show that these cells appear in the omentum before they appear in the peritoneal fluid and that their appearance is preceded by the polymorphonuclear leucocyte.

4. There is suggestive evidence that these mononuclear cells originate from the perivascular spaces of the omentum.

5. A definite time factor is involved in the development of peritoneal immunity.

6. An attempt is made to establish a rational basis for the use of certain drugs and procedures in the prevention and treatment of peritonitis.

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SECTION OF THE POSTERIOR ROOTS FOR THE RELIEF OF PAIN IN ANGINA PECTORIS

Observations in Five Cases

HALE HAVEN, M.D., and ROBERT L. KING, M.D., Seattle, Washington

FROM its earliest beginning, the practice of medicine has been dedicated to the relief of human pain and suffering. The pain of most diseases is controlled by drugs and finally relieved by a restoration of the bodily functions to normal. Unfortunately, we, as physicians, are faced with certain clinical entities in which pain may be an intractable manifestation, often uncontrollable by medical treatment, and the morbid process such as to preclude a restoration of the bodily economy. Angina pectoris may take its place in this group along with trigeminal neuralgia, inoperable cancers, and tabetic crises. Varied surgical methods have been suggested for relieving the pain in these and similar conditions. They have often been charged with empiricism. However, the record of experimental work upon the physiology of pain, a voluminous literature compiled by many investigators, is at long last leading us to more logical and more certain methods for the relief of these painful states.

Here, it is our purpose to review, briefly, the physiological basis for a surgical operation aimed at relieving the pain of angina pectoris and to report the results in 5 patients treated by this method, together with a discussion of the indications for and against its use.

Francois Frank is generally credited with being the first to suggest that severance of cervical sympathetic fibers transmitting painful impulses from the heart to the central nervous system would stop anginal pain. It remained for Jonnesco, 17 years later, to put the idea to the test and demonstrate the feasibility of surgical methods for the relief of this agonizing pain. Many surgeons followed his example, and thereafter various types of operations were performed upon the cervical and cervicodorsal sympathetic system. High mortality rates, unpleasant postoperative complications, and failure in many instances to effect complete relief were deterrants to more widespread popularity of this method (3, 6, 8, 16, 18).

In 1923, Danielopolu and Hristide proposed, but did not do, resection of the posterior roots in the lower cervical and upper dorsal region. Their proposal was based upon the theory that cardioaortic pain was always referred, hence denervation of the area of reference would relieve the pain. Also, they pointed out that such a procedure would not interfere with important centrifugal fibers. Swetlow further focused our attention upon the sensory pathways and introduced paravertebral alcohol block for the treatment of cardiac pain. He hypothesized that "constant stimulation of the small cells in the dorsal root ganglions by impulses coming from the heart is referred to the skin segments supplied by the respective ganglions, which, in turn, refer this irritation to the consciousness as pain." Cutler, in a critical review of the surgical treatment of angina pectoris up to 1927, cited the temporary nature of the relief obtained from the injection treatment and warned against "surgery unaided by vision and the use of a powerful drug like alcohol, particularly when in proximity to the delicate structures of the nervous system."

Further clinical and experimental studies by White, Sutton and Lueth, Davis and Pollock, Anrep and Segal, Ranson, and Kuntz have served to show that visceral pain is mediated by afferent neurones of the somatic system which traverse the sympathetic trunks. Their cells of origin are in the posterior root ganglia. From the heart, these fibers reach the cord by way of the upper four or five dorsal

From the Departments of Cardiology and Neurological Surgery; The Mason Clinic and Virginia Mason Hospital, Seattle, Washington.

roots bilaterally and, as White expressed it, "this is the neck of the bottle," all the sensory fibers entering the spinal cord from the heart are here nicely grouped and vulnerable to direct attack. These workers have also shown that the sympathetic system provides the vasodilator mechanism to the coronary vessels while the vagus, or parasympathetic, fibers are chiefly vasoconstrictor in their actions. Thus, it appears probable that, contrary to the hopes of some, procedures aimed at the removal of the sympathetics not only interrupt the cardiac afferents, but, to some extent, interfere with the normal vasodilator mechanism of the coronary circulation; or, it is perhaps safely said that such procedures do not specifically interrupt vasoconstrictor impulses to the heart.

In the light of present knowledge, then, the logical plan would be directed at interruption of the cardiac afferent fibers with as little disturbance as possible of important centrifugal mechanisms. Section of the afferent rami communicantes or the posterior roots of the first five thoracic segments should effectively achieve this aim. The former method entails an operation on both sides, each of which is almost as grave as the single procedure necessary to section the posterior roots bilaterally. Paravertebral alcohol block interrupting the sensory pathways at the level of the former procedure is perhaps not without effect upon the centrifugal pathways. This method meets with failure about one-fourth of the time (19, 20), and, in addition, although it has recently been controlled to some extent by the use of vitamin B, the resultant neuritis has been a troublesome complication in a number of our patients. We have been inclined to believe with Cutler that direct vision methods produce more reliable results.

As for the operation directed at section of the thoracic posterior roots, we believe that there now can be little question of its logic or the results achieved. As previously mentioned, it was suggested by Danielopolu in 1923. Ranson noted that in 1926 Sachs had cut the sensory roots of the first four thoracic nerves on the left side and thus obtained relief in a case in which characteristic anginal pain had recurred after removal of the cervical sympathetic ganglion. Davis is to be credited with being the first to carry out successfully the operation of bilateral posterior root section in a case of angina pectoris. Cone is also reported to have performed this operation in two cases (19, 20).

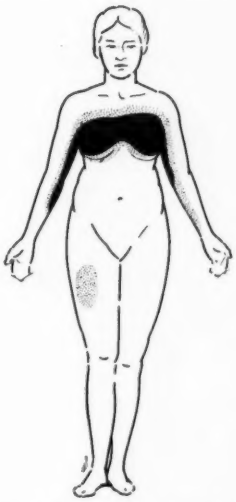

Fig. 1. Diagram of the sensory loss following operation in Case 1. The stippled area in the thigh is the hyperesthetic zone mentioned in the text.

There has been some criticism of many of the reports in the literature on the surgical treatment of angina pectoris (4, 5), and Boas stresses the necessity of differentiating between various types of cardiac pain and true angina pectoris. Also, many authors have felt that the pain of angina pectoris is a warning to the individual to slow up and that the removal of this danger signal is unwholesome.

Naturally, radical measures such as alcohol injection or operation should be used only in those obstinate cases in which the pain persists in spite of ample medical measures and is of such a degree as to render work impossible and life miserable. The selection of cases is, therefore, most important and should be limited to those patients having intractable anginal syndromes. The following cases, we believe, meet these requirements and permit a fair evaluation of the method, a clinical verification of some of the experimental work upon which the procedure is based, and some

Fig. 2a.

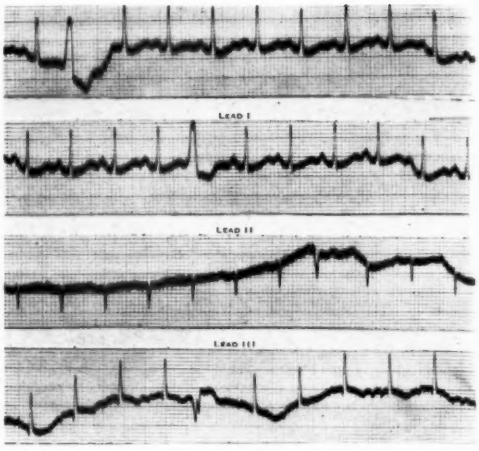

Fig. 2b.

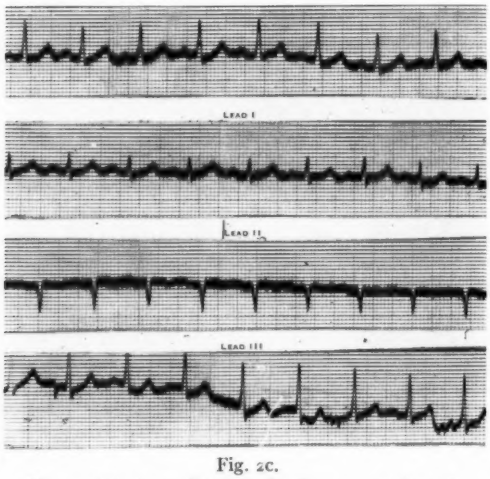

Fig. 2c.

Fig. 2. Electrocardiograms in Case 1. a, August 14, 1936, before operation; b, September 18, 1936, the first postoperative day; c, March 14, 1941, 4½ years after operation. Note changes in chest leads referred to in the text.

observations upon the reference of anginal pain.

CASE 1. No. 59851. Hypertensive and arteriosclerotic heart disease with previous coronary thrombosis resulting in angina pectoris; pain not controlled by bed rest and excessive opiates; section of upper thoracic posterior roots; patient converted from bedridden invalid to a person of almost normal activity for her age.

Mrs. E. M., age 55 years, the wife of a retired realtor, was first seen on August 14, 1936. Her mother and grandmother had died of heart disease. She had had no pregnancies and, except for an appendectomy in 1918, had always been well until September, 1933, when she contracted pneumonia from which she completely recovered in 3 to 4 weeks.

In December, 1933, while eating breakfast, she was suddenly seized with a sharp substernal pain which was accompanied by a sense of impending disaster, causing her to "freeze and squirm in my chair." She was immediately hospitalized and remained in bed for the next 5 months; during that period she required many hypodermic injections for control of her pain which continued to recur while she was at rest. The pain radiated to the left arm and, when quite severe, was also noticeable in the right thigh. She was up and about in May, 1934, but continued to have attacks of pain necessitating narcotics hypodermically at intervals of 1 or 2 weeks. On several occasions, the anginal attacks caused her to collapse in the street. She became unable to climb the stairs to her bedroom so an elevator was installed in the house for her convenience. Finally, even the ride in this seemed to precipitate an attack. In May, 1936, sympathetic injection was contemplated at another clinic, but it was discouraged because of the seeming severity of her condition. From then on, increasing doses of narcotics were given to make her comfortable. For some time, she had remained bedfast at home, receiving 1/16 grain dilaudid every 4 hours. There was some question of addiction, but she continued having attacks at the slightest exertion coupled with moving herself about in bed, and she voiced a sincere desire to be rid of the necessity of taking "dope."

Examination. The patient was a slightly apprehensive, well nourished woman, 64 inches tall, weighing 143 pounds, who appeared older than her stated age of 55. There was some hyperesthesia of the skin over the left breast and precordium in gen-

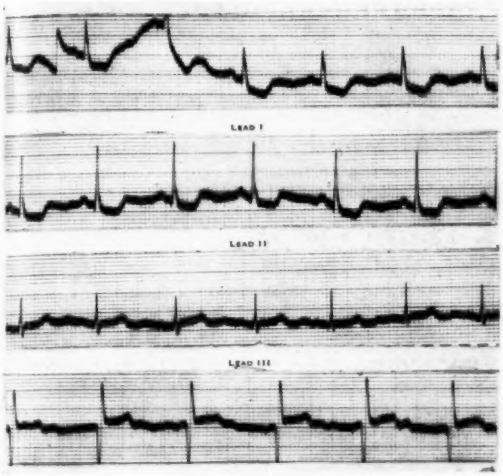

Fig. 3a.

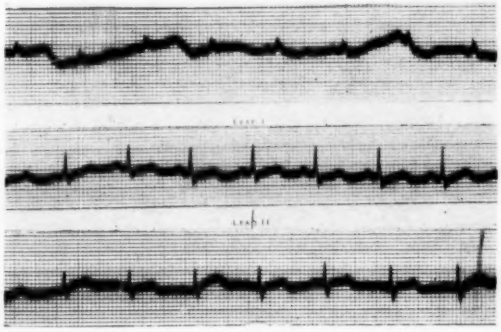

Fig. 3b.

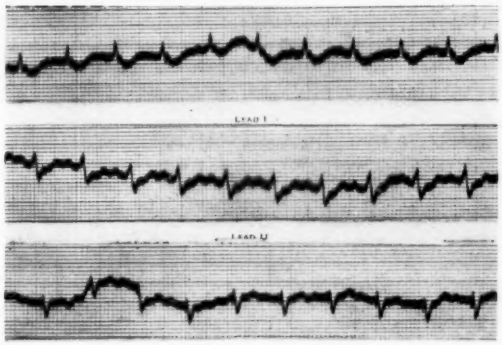

Fig. 3c.

Fig. 3. Electrocardiograms in Case 2. a, February 16, 1937, before operation; b, March 6, 1937, the first postoperative day; c, March 8, 1937, third postoperative day with evidences of new cardiac infarction.

eral. No cardiac murmurs were audible, and the heart rate was 76 with an occasional extrasystole. The blood pressure was 190/88, the temperature 97.6 degrees F.

Laboratory studies revealed that the blood and urine were normal. The blood Kolmer and Kahn tests were negative. X-ray studies of the gastrointestinal tract and gall bladder revealed no pathological condition. A teleoroentgenogram revealed the heart to be of normal size and contour. The lung fields were clear. Venous pressure was 110 millimeters of water. The vital capacity was 2.3 liters. An electrocardiogram showed a rate of 96 and a *P-R* interval of 0.2 of a second; there was a tendency toward left axis deviation, Q_4 was absent (original technique of Wolferth and Wood)[1], T_3 was inverted, T_4 was isoelectric, and T_1 and T_2 were upright. These findings were regarded as probably indicative of previous cardiac infarction.

Observation of this patient from August 14 until September 17, 1936, showed that satisfactory relief could not be obtained by the use of many varied vasodilating substances. Only ever increasing doses of opiates were successful in alleviating the pain. On one occasion, when a severe attack was in progress and the complaint of pain in the right thigh was particularly distressing, the subcutaneous tissues of the area of reference in the thigh were infiltrated with 1 per cent novocain. This relieved the pain in that area, but the attack continued unabated in the chest and left arm. There was some fear that there might be a major functional element in this patient's complaints, but after long study we were convinced that these attacks were cardiac in origin and truly anginal in character and that surgical therapy was justified.

Operation was performed on September 17, 1936. Basal anesthesia of avertin, 100 milligrams per kilogram, was given at 8:50 a.m. Local infiltration of the skin and muscles with 1 per cent novocain followed, and a laminectomy with removal of the spines and laminae of the first four dorsal vertebrae was done. The dura was opened, and the first, second, third, and fourth thoracic posterior roots on the right side were severed. On the left, the first, second, third, fourth, and fifth thoracic posterior roots were cut. The dura was closed with interrupted silk sutures, and the muscles, fascia, and skin approximated in the usual manner without drainage. There had been no appreciable change in the blood pressure throughout the operative procedure; and, while cotton pledgets moistened with novocain had been placed over the individual roots previous to their being handled, this did not serve as sufficient analgesia,

[1]In our laboratory from 1933 to January 1, 1938, the technique employed for taking chest leads was as follows: The right arm wire was attached to an electrode 3 centimeters in diameter which was placed over the apex cordis. The left arm electrode was placed between the midline of the back and the angle of the left scapula. Subsequent to January 1, 1938, all chest leads were made according to the recommendations of the Committee for the Standardization of Precordial Leads. Lead *IVF* has been employed for general use.

Fig. 4. The massive myocardial infarct in Case 2.

and a few whiffs of ether were necessary during this part of the procedure. The patient was awake and co-operative upon completion of the operation. She frankly stated that she really felt better than at the start.

Subsequent course. This patient made an uneventful and uncomplicated recovery. She did not request any sedative following operation. Her only complaint of discomfort was an occasional dull backache below the area of operation. For 3 days following operation, her pulse rate varied between 120 and 140. An electrocardiogram revealed this to be a sinoauricular tachycardia (rate 120) without other significant differences from the previous tracing. On the 4th postoperative day, the pulse rate returned to below 80. She was discharged from the hospital on the 8th postoperative day, walking and free from pain.

She returned on November 16, 1936, for observation. She appeared to be in good general condition, had had no anginal attacks, and was, according to her, leading a rather normal existence with only slightly limited activity. Neurological examination at that time revealed only the sensory loss over the areas subserved by the sectioned dorsal roots. It had the typical pattern of a root lesion at its borders. An electrocardiogram then showed a rate of 96 and, otherwise, the same findings as were noted before.

On March 14, 1941, this patient responded to our request that she come to Seattle for a check-up. At this time, she reported that she had been generally well and had consulted no physicians since her last visit to the clinic. She had taken no medicines or drugs except an occasional laxative. There was some fatigue at the end of the day, and, after the exertion of climbing a number of stairs, she had some dyspnea but no pain. There were some paresthesias noticed at times in the denervated area, the borders of which were unchanged from 1936. Since her operation, she had engaged in the usual activities of her social group without apparent stint. She had made a four thousand mile motor trip with her husband and had gone through a week of 100 to 114 degree temperatures in the southwestern states with no more than average trouble.

Clinical examination at this time showed the left border of cardiac dullness to be at the midclavicular line. Heart sounds were of fair quality with a gallop barely audible over the mitral area. The pulmonic and aortic second sounds were equal. The blood pressure was 220/120. The extremities showed no edema, and the liver was not palpable. Laboratory studies of the blood and urine were within normal limits. The venous pressure was 92 millimeters; vital capacity 1.7 liters. The circulation rate with calcium gluconate and ether was: arm to tongue 13 seconds; arm to lung 10 seconds. A teleoroentgenogram showed a heart of normal size and contour. The lung fields were clear. An electrocardiogram showed a rate of 108, a *P-R* interval of 0.2 of a second, a sinus rhythm, and a tendency toward left axis deviation; the *T*-wave in lead *IVF* was upright, which corresponded with the inverted *T* of the technique of the 1936 tracings; R_4 was normal. This finding is noteworthy in that the corresponding Q_4 was absent in the 1936 tracings obtained by the earlier technique.

CASE 2. No. 48061. Arteriosclerotic heart disease with angina pectoris of seven years duration; previous coronary thrombosis; pain uncontrolled by rest or medical means; operation followed by relief of pain; death fourteen hours after new coronary occlusion causing massive cardiac infarction unaccompanied by pain; autopsy.

Mrs. H. P., aged 52 years, the wife of a farmer, was first seen on July 5, 1933. Both her parents had died of the infirmities of age. There was no familial history of cardiac or renal disease. One tube and her appendix had been removed in 1921, and a tonsillectomy was performed in 1929. She had suffered from arthritis at various times for about 30 years. At that time, she complained of pain which radiated down the inner aspects of both arms from the shoulders to the hands. This was precipitated and aggravated by exertion. It seemed to be associated with other arthritic manifestations, and there were no special symptoms referable to the heart. Her blood pressure was 150/85, her pulse 50 and regular, and her heart tones normal. Both antra transilluminated poorly and were cloudy on x-ray examination. They were drained and irrigated. In August, 1933, she reported that she was much improved but on exertion would occasionally suffer a pain beginning in the left wrist, radiating upward and across the chest to the precordial region. She was not seen again until February 16, 1937, when she was admitted to the hospital complaining of pain on the inner aspect of the right arm on the slightest exertion. She then stated that these pains had been present intermittently 7 years before. The pain on the left side had been relieved with the administration of amidoxyl in 1933. The pains were always precipitated by exertion and relieved by rest. At times, there was radiation of the pain to the epi-

gastrium and an associated shortness of breath. There had been a constant increase in the frequency and severity of the attacks. Considerable medical treatment, administered by several different physicians, had been ineffective. She had suffered intense pain since the evening before, and, on admission, the slightest movement of her body caused an increase of the pain. For some period of time, any undue excitement or even the slight exertion of making a bed, had been sufficient to precipitate an attack.

Examination. The patient's development and nourishment were normal. She weighed 123 pounds. Her lungs were normal to auscultation and percussion. The heart borders were indeterminate. A systolic murmur was heard at the apex. The blood pressure was 120/80. The pulse rate was 75. Urinalysis, blood counts, and serology were normal. X-ray film of right shoulder showed no arthritis. A cholecystogram was normal. Teleoroentgenogram of the chest showed clear lung fields, and a cardiac shadow which was within normal limits. The venous pressure was 90 millimeters, and the vital capacity, 2.3 liters. An electrocardiogram showed a rate of 72, a *P-R* interval of .18 seconds, and positive T_4 and depressed *S-T* interval in leads I and II, which was suggestive of digitalis effect.

The patient was seen by a number of our internists, and the conclusions at this time were that she had arteriosclerotic heart disease and angina pectoris. The interesting feature of a right-sided angina was noted. While at rest in the hospital, she continued to have pain. Occasionally, nitroglycerine afforded temporary relief, but frequent recourse to narcotics was necessary to control the anginal attacks which would, at times, come spontaneously or be precipitated by the effort required to turn while her bed was being made up. After more than 2 weeks in the hospital, all medical measures seemed doomed to failure, and the patient requested more certain relief.

Operation was performed March 5, 1937. Preliminary medication of morphine sulfate, ¼ grain, and atropine, 1/150 grain, was followed by a basal anesthesia of avertin, 100 milligrams per kilogram. One per cent novocain was infiltrated in the subcutaneous tissue and muscles, and a laminectomy of the first four dorsal segments was performed. The dura was opened, and the first five thoracic posterior roots were secured on each side and cut between Cushing clips. There was slight oozing of blood from the dura near the exit zone of the third root on the right, which was easily controlled with a small muscle stamp. The dura was sutured with interrupted silk, and the wound was closed without drainage in the usual manner. The blood pressure, which had been 120/80 previous to operation, fell to 80/60 at the beginning of the operation but, with the stimulus of surgery, rapidly regained a satisfactory level, about 115/70, where it remained until her return to the ward in seemingly good condition at the close of the operative procedure.

Subsequent course. This patient's immediate reaction following the operation was satisfactory. The first 2 days following operation, she was exceptionally comfortable, suffered none of her old pain, and moved about in bed freely without precipitating any attacks. Her blood pressure varied from 90/50 to 120/80, and on the second postoperative day she felt so well, she decided to do without her special nurses. On March 6, an electrocardiogram was made. It showed the rate to be 96. The *P-R* interval was 0.18 of a second. There was less depression of the *S-T* interval in lead I, and no depression in lead II as compared with the tracing made on February 16. The patient had not received any digitalis in the interval. There was no evidence of cardiac infarction. Early in the morning of March 8, the third postoperative day, she suddenly complained of a peculiar feeling of tightness across the chest which, she insisted, was not painful. She became nauseated and vomited. A little later, she felt as though she were short of breath, but she could inhale deeply, etc., without difficulty and her respiratory rate was not increased. Her blood pressure suddenly dropped to 60/?. Her pulse had jumped from 90 to 130 and was weak and irregular. Her temperature was not elevated. Her venous pressure had risen to 98 millimeters. An electrocardiogram showed a rate of 120, a *P-R* interval of 0.18 of a second. The *S-T* intervals in leads I and II were depressed; aberration of *QRS* was marked, and there was a lowering of potential in all leads. When compared with the tracing of March 6, it was considered that an acute cardiac infarction had occurred. In spite of the oxygen and cardiac stimulants, she succumbed about 14 hours after the apparent acute inception of this latest coronary episode. To the last, she was seemingly clear mentally and most co-operative. She insisted at all times that she had no pain but a certain knowledge that something was wrong in her chest. This she variously described as a peculiar sense of tightness, a feeling of pressure over the precordium, or a feeling as though she could not get her breath although, at the same time, she realized that she was breathing regularly and at a normal rate.

Postmortem examination. The body had been embalmed shortly after death, and the autopsy was performed 2 hours later. Marked adhesions of the abdominal viscera resultant from the ancient laparotomy were found. There was also pulmonary edema and acute passive hyperemia of the liver and spleen. The heart weighed approximately 400 grams. Practically all the interventricular septum and the wall of the left ventricle appeared to be involved in a fresh process of infarction. The valves and cusps of the heart were free of gross alterations. The coronary vessels were markedly sclerotic. The descending branch of the left coronary was practically obliterated by calcareous deposits in the wall of the vessel. Near its point of origin, it was completely occluded by a red-purple thrombus. All the coronary vessels were brittle and, in cutting across them

with the knife, a sensation of stone-like hardness was detected. The lining of the aorta was approximately 50 per cent changed by yellow atherosclerotic plaques.

CASE 3. Anginal attacks of 3 years' duration; paravertebral alcohol block on the left followed by temporary relief; recurrence of symptoms; posterior root section with return to employment.

Mrs. H. S., aged 39 years, who was married 10 years and a graduate nurse, was first seen in November, 1937, when she was referred to the Clinic by a local internist for a paravertebral alcohol block. She knew little of her antecedents. She had suffered severe headaches as a child which were relieved by wearing glasses while in school. Her appendix had been removed when she was 11 years of age, and, when 31, she had passed a kidney stone after an attack of hematuria.

In 1935, she had suffered a sudden attack of precordial pain radiating to the left arm and, at times, to the left leg. This occurred while she was working as a nurse. She was in bed for 4 months' rest thereafter. Electrocardiograms taken at that time were said to have been inconclusive. Many lesser attacks were experienced thereafter at times of increased activity or emotional upset. In March, 1936, she had been referred by her local physician to the clinic laboratory for an electrocardiogram which showed: rate 72, *P-R* interval 0.16 of a second, a tendency toward left axis deviation, and a moderately low potential; it was otherwise normal.

In October, 1937, she had suffered an unusually severe attack while preparing breakfast. An oppressive, squeezing, precordial pain, which radiated to the left arm and was relieved only by large and frequent hypodermics of opiates, had persisted since that time. A loss of consciousness was said to occur when the pain was most severe, and the husband reported a slowing of her pulse to 38 on these occasions. This was never confirmed.

Examination. The patient appeared to be small and prematurely aged but not emaciated. She was 5 feet tall and weighed 92 pounds. Her hair was iron-gray, coarse and dry. Heavy black hair was found on the upper lip and on the chest about the nipples. The pubic hair extended to the umbilicus in a masculine configuration, and there was a profuse growth of dark hair on the thighs and lower legs. There was a small nodule palpable about the middle of the thyroid isthmus. Her breasts were small and atrophic appearing. The lung areas were resonant, and breath sounds were normal. Heart borders and tones were within normal limits. The pulse rate was 74; the blood pressure 120/80. Neurological examination revealed physiological responses throughout.

Laboratory studies revealed the blood and urine to be normal. The serology was negative. An electrocardiogram then showed a rate of 72, a *P-R* interval of 0.16 of a second, and a tendency toward left-axis deviation with a small Q_4 and isoelectric T_4.

On November 19, 1937, following the injection of novocain to verify the position of the needles, 3 to 5 cubic centimeters of absolute alcohol were injected into the region of the sympathetic rami beneath the first, second, third, fourth, and fifth ribs on the left side. A mild Horner's syndrome and anesthesia over the respective dermatomes was obtained.

The patient remained in the hospital for 2 days following the alcohol injection, during which time she was free of pain. She was then discharged to the care of her local physician. On December 28, 1937, she was readmitted to the hospital complaining of neuritic pains in the anesthetic area about the left chest and a loss of weight of 10 pounds. Her anginal attacks had not reappeared. She was given large amounts of vitamin B_1 and a high calorie diet and was discharged improved after a week's stay.

When next seen on May 2, 1938, this patient stated that after the disappearance of the neuritis in January, 1938, she felt better than she had for 20 years until mid-February when a mild precordial pain was noticed on a few occasions coincidental with a return of sensation in the previously anesthetic zone. These attacks were similar to her previous anginal seizures and increased in severity and feqeuency until in March she had been forced to her bed again where she had remained, getting up only on rare occasions. At first, she had taken codeine, amytal, and nitroglycerine with some relief, but more recently these failed and large doses, ½ grain, of morphine were needed to ease the pain during the attacks which were coming three or four times daily and lasting at times for several hours.

Examination. There were no notable deviations from the previously recorded physical findings at this time. The blood pressure was 138/100, the pulse 72. The lungs were resonant with normal breath sounds, and the heart tones were normal. The laboratory studies of the blood and urine showed them to be normal. The venous pressure was 65 millimeters. A teleoroentgenogram of the chest revealed no abnormalities. The electrocardiogram now showed a rate of 84, a *P-R* interval of 0.17 of a second, a definitely lowered potential, and a normal lead *IVF*.

Operation was done on May 4, 1938. After preliminary medication of one hyoscin-morphin-cactin No. 1 and local infiltration of 1 per cent novocain incision was made over the spines of the 7th cervical to the 4th dorsal vertebrae, inclusive, and the spines and laminae of the 1st, 2d, and 3d dorsal vertebrae were removed with the rongeur. No difficulty was encountered over the removal of the laminae on the right side, but on the left there was marked oozing from vessels in the extradural fat. When the laminectomy was completed, a plexiform arrangement of veins was noted extradurally on the left side which extended around the left lateral aspect of the dura as far as one could easily follow them. The veins over the left dorsolateral aspect were ligated with silver clips. The dura was opened, but no evidence of intradural extension of this vascular anomaly was found. The 2d, 3d, 4th, and 5th thoracic posterior roots on the left side were secured between clips and

severed. The 1st root on the left could not easily be cut because of its position in the upper part of the incision so it was crushed with a hemostatic forceps. The first five thoracic posterior roots on the right were crushed with a hemostat but were not severed. The dura was closed with interrupted silk sutures, and the rest of the wound was closed in the usual manner. The patient withstood this procedure well and was returned to her ward in good condition with an anesthetic zone corresponding to the roots which had been cut or crushed during the operation.

Subsequent course. Convalescence was uneventful. No narcotics were needed nor requested by the patient. She was discharged from the hospital on the 7th postoperative day free of her pain. She remained free of anginal attacks and resumed her nursing during the summer of 1938. In September, 1938, according to her local physician, she suffered an attack of severe headaches, backache, and mild fever, accompanied by a marked drowsiness. A spinal puncture was done, but the fluid was found to be normal. Influenza was diagnosed. She made an uneventful recovery, and, when last heard from in the summer of 1939, was working as a supervisor of nurses in a distant village hospital.

CASE 4. No. 73210. Arteriosclerotic heart disease with angina pectoris; response to medical treatment not sustained; posterior root section; freedom from attacks thereafter, permitting resumption of part of former duties.

Mr. C. H., a dairyman, 60 years old, was first seen on November 21, 1939. His mother and one brother had died of heart disease. He had previously enjoyed excellent health and had always worked hard on his farm until 6 weeks before, when he was forced to stop work because of severe chest pain. He had first noted a shortness of breath on exertion 3 years before. This was accompanied by a burning sensation over the precordium which was relieved if he stopped to rest. There had been a gradual increase in the frequency and severity of these attacks. More recently, the pain had occurred several times while he was at rest. It was oppressive in character and radiated down both arms, being most marked in the right. Also, there was, at times, a radiation to the neck and up behind both ears. A drink of whiskey afforded relief on occasion. There was some palpitation. He had consulted two physicians concerning his heart and had been given medicine which had no influence on the pain. For 6 weeks, he had confined himself to the house because of the pain which was precipitated by walking even a short distance on the level. He stated rather frankly that he was almost entirely useless as far as even the supervision of his farm was concerned.

Examination. He was a stocky, well developed, slightly obese individual, 67½ inches tall, weighing 174 pounds. The lungs were resonant throughout. The breath sounds were normal. The heart borders were within normal percussion limits, the tones of good quality, and the rhythm regular; no murmurs

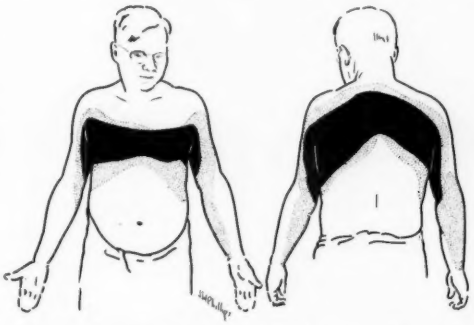

Fig. 5. Case 4, 14 months following operation. The area of sensory loss is marked on the skin within the dotted line; both touch and pain sense are absent. Pain sense alone is absent in the area between the dotted and continuous lines.

were heard. Blood pressure was 120/80, pulse rate, 70; abdominal and rectal examinations negative; no abnormalities of neurological function present.

The blood picture and serology were reported as normal. Repeated urinalyses revealed no pathological findings. The venous pressure was 78 millimeters. Circulation time was: arm to lung, 5 seconds; arm to tongue, 14 seconds. Roentgenograms of the chest showed clear lung fields and a normal-sized cardiac shadow. An electrocardiogram revealed a rate of 72, occasional ventricular extrasystoles, a *P-R* interval of 0.2 of a second, and a tendency toward left axis deviation; the *T*-waves were low in leads I and II, inverted in lead III, and isoelectric in lead *IVF*.

He was under observation in the hospital for 2 weeks. In this time, he had severe anginal attacks on the slightest exertion. They could be relieved by nitroglycerine, but there was not sufficient sustained relief on medical management to permit him any appreciable amount of activity. It was his opinion that almost anything was preferable to the state of invalidism that he was in. In view of the seemingly competent heart and his good general condition, we felt justified in recommending operation.

Operation was performed on December 1, 1939. With preliminary medication of one hyoscin-morphin-cactin No. 1, and local infiltration with 1 per cent novocain, a laminectomy was performed on the first 4 dorsal vertebrae. The dura was opened and the first 5 thoracic posterior roots in each side were individually lifted up with a blunt hook and crushed between the jaws of a pointed hemostat. Just previous to manipulation of the roots, a cotton pledget moistened in novocain was placed upon each and this resulted in a satisfactory anesthesia. The dura, muscle, and cutaneous structures were closed in the usual manner without drainage.

Subsequent course. This patient had an exceptionally uneventful convalescence. He was discharged, walking, on the 11th day.

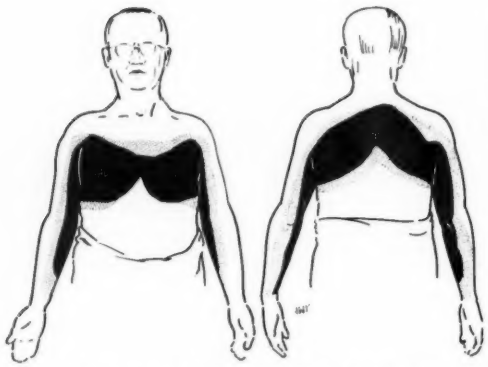

Fig. 6. Case 5, 2 weeks after operation, showing boundaries of area of sensory loss. The dotted area represents the overlap of touch sense as is usual in a root lesion.

On January 10, 1940, a month after leaving the hospital, he reported for follow-up studies. He had experienced none of his old anginal attacks but noticed at times a sense of substernal oppression on exertion. He then weighed 177 pounds. His pulse was 76, the blood pressure 130/90. There was no evidence of congestive heart failure. On auscultation, the rhythm and quality of the heart sounds were normal. The vital capacity was 2.9 liters. An electrocardiogram showed a rate of 60, regular mechanism, a *P-R* interval of 0.16 of a second; T_1 was upright, T_2 slightly diphasic, and T_3 inverted; lead *IVF* was normal. The changes over the previous tracing were not considered significant.

On February 26, 1940, this patient reported that he had extended his activities to supervision of the work about his farm. He could walk the quarter-mile to his mail box and back to the house without symptoms, but on heavier exertion, he noticed a feeling of fullness in the neck and chest. His vital capacity was 3.1 liters.

On March 19, 1941, he came in upon request for follow-up studies. He stated that he had been generally well and was able to do approximately one-third of his former work. In August, 1940, he had made a transcontinental motor trip. He drove the car a good part of the distance and had felt no untoward effects from this adventure. His activity was restricted only by a sense of fatigue and a substernal constriction. He had no pain at any time. In the event that he engaged in too much carpentry or milked more than 8 cows in an evening, he would feel rather weak for 2 or 3 days.

On examination, then, the area of sensory loss conforming to the root lesion of the upper five thoracic roots on both sides was essentially the same as upon his discharge from the hospital. He weighed 173 pounds. The pulse rate was 68, the blood pressure 130/80. The lungs were clear, the heart was of normal size, and the tones were normal. The liver edge was barely palpable. There was no edema of the extremities. He had taken no drugs and received no medical care since his last visit to the clinic. Blood counts were normal. The venous pressure was 106 millimeters, and the vital capacity 3.3 liters. Circulation time was: arm to tongue, 17 seconds; arm to lung, 6.5 seconds. An electrocardiogram showed a rate of 72, regular mechanism, a *P-R* interval of .2 of a second; T_1 was upright, T_2 was flattened, and T_3 inverted; lead IVF was normal. When this was compared to previous tracings, there was no significant difference.

Case 5. No. 74706. Arteriosclerotic heart disease with somewhat atypical anginal syndrome, uncontrolled by rest or medical management; temporary relief following paravertebral block with novocain; posterior root section with effective relief and return to useful activity.

Mr. R. L. S., a 61 year old sawmill operator from an isolated Alaskan community, was first seen March 11, 1940. A brother had died suddenly at the age of 68 of a heart attack. Except for an inconsequential head injury in 1916, he had always been well. For 5 years, he had been operating a small sawmill which necessitated his doing part of the work himself. In 1936, while doing some heavy lifting at his mill, he was suddenly seized with a severe pain between the shoulder blades. It radiated through the chest and around the thoracic wall on both sides. It was not of a crushing character. There was some dyspnea, but he was able to walk some few blocks to his home. The pain lasted 18 hours before a physician was called. Then two hypodermics were required for relief. Thereafter, he avoided strenuous exertion, and it was several months before the pain recurred. Then there was a gradual increase in the frequency and the severity of the anginal attacks. Always, the onset of the pain followed exertion or excitement. He could not walk more than 75 or 100 yards on level ground without experiencing the pain. Rest gave him relief and enabled him to continue on. No narcotics had been necessary after the first attack. The pain at times radiated into the neck and down both arms, more often the right than the left. On a number of occasions, he had been awakened at night with the pain and had to raise up in bed in order to obtain relief. There had been no symptoms suggestive of congestive failure. A clinical diagnosis of probable aortic aneurysm had been made elsewhere.

Examination. He had an exceptionally well developed, muscular build, was 68 inches tall, and weighed 192 pounds with only a trace of obesity. The lungs were clear, the heart borders within normal percussion limits, and there was no detectable increase in aortic dullness. The heart tones were normal, the rhythm regular. The pulse rate was 84; the blood pressure 140/85. There were no clinical manifestations of organic disease of the nervous system.

Laboratory studies revealed a normal blood picture. The serology was negative. The urine was normal. The venous pressure was 78 millimeters. The circulation time was: arm to tongue, 16 seconds;

arm to lung, 4 seconds. The vital capacity was 3.5 liters. X-ray examination of chest revealed the heart to be of normal size and contour. The aorta appeared to be normal in both posteroanterior and lateral views. X-ray films of the dorsal spine, the stomach, duodenum, and gallbladder showed no abnormalities.

An electrocardiogram revealed a rate of 72, regular mechanics, a *P-R* interval of 0.21 of a second; the *QRS* complex in lead III was of the *W* type with a suspiciously deep *Q* wave. T_3 was isoelectric. The possibility of a previous posterior infarction was considered.

This patient was placed on medical management and carefully followed. It gradually developed that he was having a great deal more pain than he at first intimated. Not only did he have attacks upon walking one to two hundred yards on a level, but he was distressed several times each night. Nitroglycerine afforded some relief but was not at all satisfactory to the patient. A trial with erythroltetranitrate and phenobarbital therapy did not serve to relieve him. A paravertebral block with novocain in the region of the upper four thoracic sympathetic ganglia on both sides was then performed. Following this, he was able for the first time to walk the four blocks from the clinic to his room without pain and without resting. He estimated that he was 90 per cent relieved during the period the novocain was effective. He was well pleased with the result and, after further trial on medical management, requested more permanent relief.

Operation was performed on April 27, 1940. After preoperative medication of hyoscin-morphin-cactin No. 1, under local anesthesia, a laminectomy was performed in the upper dorsal region, the spines and laminae of the first four thoracic vertebra being removed. The dura was opened and, after a pledget of cotton moistened with novocain was placed upon the roots for a few minutes, the posterior roots of 1st, 2d, 3d, and 4th dorsals on the right and 1st, 2d, 3d, 4th, and 5th dorsals on the left were individually raised on a blunt hook and crushed between the jaws of a hemostat. The dura was closed; because of some little oozing from the heavy muscles in this patient's back, a Penrose drain was left in the wound on closure of the muscles and skin. This was removed 24 hours later.

Subsequent course. The second day after operation, this patient developed a cough and a slight elevation in temperature. He was thought for a time to be developing pneumonia. This condition soon cleared, and he made a rather uneventful recovery. He had none of his old pains while in the hospital. There was a loss of sensation over the skin area represented by the sectioned roots. He was discharged from the hospital on May 16, 1940. On May 30, 1940, he reported that he was able to walk ten blocks without any distress. He had noticed an old headache which had bothered him off and on for many years and would become noticeable if he exerted himself too much or became unduly excited. His blood pressure was 180/70, the pulse 80. An electrocardiogram showed an occasional ventricular extrasystole, a rate of 72, and a *P-R* interval of 0.22 of a second. There were no significant changes over the previous tracings.

He left for his home in Alaska in June, 1940, and has not been examined since; however, in response to a letter of inquiry in March, 1941, he wrote at length regarding his condition at that time. He noticed at times of undue exertion some mild pains about the shoulders and back and "peculiar feeling bordering on pain seems to radiate to the head. This cannot be described as a pain but starts as a sort of dull, clouded sensation, quickly becoming almost like an ache at the base of the skull and back of the eyes particularly, but enveloping the whole head, giving one the feeling that anything can happen and probably will. . . . I could almost say that there is no symptomatic feeling of constriction or anything of that kind in the chest that amounts to anything. . . . I like to putter around the house and I find that I can perform work such as sawing slabwood in two with an ordinary hand-saw and have kept the furnace going all winter with wood cut in this way and all pretty much by my own labor. Shovelling snow and many other chores at which I can take my own sweet time don't bother me at all. A year ago, those things were impossible." His local physician at that time noted as a postscript to the patient's letter: "Blood pressure 120/80, heart regular, pulse normal, no pain around chest, some pain in neck and back in case of overexertion."

We are acutely aware of the difficulties encountered in arriving at an accurate diagnosis in some cases of angina pectoris, and we have always adopted a skeptical attitude in interpreting pain of possible cardiac origin. This attitude is proper, especially when the pain has an atypical pattern or whenever the repeated administration of narcotics has been necessary, but in spite of it, this group of patients convinced our numerous associates as well as ourselves that they had true angina pectoris of a completely disabling character.

It is noteworthy that in the group selected for operation, objective evidences of heart disease were not extreme. An appreciable amount of congestive failure was lacking in all. Only in Case 1 was there characteristic evidence in the electrocardiogram of a previous cardiac infarction. In the other cases, the electrocardiographic evidence of previous coronary episodes was less conclusive. In only 2 instances were there any significant differences between the tracings made before and after operation. In Case 1, Q_4 was absent before

operation. Subsequently, this component became evident. This might be interpreted as proof of an improved condition of the myocardium. In Case 2, the clinical impression of a painless postoperative coronary thrombosis was substantiated by the electrocardiogram and was verified by autopsy.

Reference to the historical details of the individual cases shows that for the most part the character and radiation of the pain was fairly typical. The fact that in Case 1, the patient in addition to a typical left-sided anginal pain also had pain in a sharply delimited area on the right thigh is interesting, as is the fact that novocain administered subcutaneously in this area relieved the pain in the thigh while it continued unabated in the left chest and arm. In the rare intervals that this patient was free of pain before operation, there was a cutaneous hyperesthesia of mild degree over this area in the thigh, and for about 1 week following the operation there was a slight hypoalgesia over the same area. At the time of her last examination, this area could not be demarcated. All patients, of course, had a permanent sensory loss over the area subserved by the destroyed posterior roots. The area in which there was loss of sensibility to painful stimuli was greater in each instance than that in which there was loss of the sense of touch. Only 1 patient, Case 5, seemed at all disturbed by subjective paresthesias in the anesthetic areas, and he mentioned them as minor annoyances.

To the best of our knowledge, of the 4 patients who have now been followed from 1 to almost 5 years, none has had any semblance of painful anginal attacks since the operation. Each has, however, some definite subjective manifestation that warns him when he reaches his tolerance of exertion. This seems in general to be a vague sense of fullness in the neck and chest, with an accompanying feeling of apprehension. In reference to Case 2, we recognize the uncommon occurrence of even extensive cardiac infarction without pain. But, we believe it unlikely for one to live as long after the accident as this patient without more acute subjective distress than she had. It is further emphasized that she, too, had the afore-mentioned "warning signal."

The question of improvement of coronary circulation by such procedure as has been carried out in these cases is, of course, interesting, involving as it does the question of the vasomotor control of the coronary vessels and the possible vicious circle phenomena sustained by the pain. Concerning this, we may call attention to the fact that in all the cases followed, there was definite and marked improvement in the tolerance for exercise. Each of them can now do more before noting the "warning signal" than he could previous to the operation before experiencing pain. We can only suggest that this may be evidence of coronary circulation improvement.

In light of the above observations, it seems to us that the intradural section of the first five thoracic posterior roots effectually severs all cardiac afferent fibers concerned in the production of anginal pain. The operation can be performed largely with local anesthesia, and in our hands it does not seem to be as shock-producing as an equivalent paravertebral rami section. The only fatality in this series was a patient with a consistently low blood pressure and a high degree of arteriosclerosis. We may consider that such a combination constitutes a contraindication to the use of this procedure. We would also consider any marked degree of congestive heart disease a contraindication. Nor do we believe that patients who can be controlled by medical means with any degree of satisfaction should be subjected to this operation. Alcohol injection is, without doubt, a safer procedure and is still to be preferred in most instances; however, for those patients with intractable angina pectoris in whom alcohol injection is unsuccessful and for that small group of exceptionally favorable risks in which one desires to avoid the 25 per cent chance of a poor result following alcohol injection, we believe this procedure to be the method of choice.

CONCLUSIONS

The records of 5 patients who were subjected to an intradural section of the upper thoracic posterior roots on both sides for the relief of intractable angina pectoris are presented. One patient died following operation, a case and operative mortality of 20 per cent.

The remaining cases were followed for periods of from 1 to 4½ years. None have had recurrences of their pain. All have had an increase in tolerance to exercise, and all have adequate "warning signals."

Caution is advised in the selection of cases for this type of procedure.

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THE WOUND HORMONE CONCEPT IN WOUND HEALING

ELTON S. COOK, Ph.D., and JOHN C. FARDON, M.S., Cincinnati, Ohio

IN this paper we wish to indicate briefly the position of chemical substances, produced by injured living cells, as the possible natural stimulus, or so called "formative stimulus," to wound repair; and, in particular, to relate certain studies carried on in our laboratories of this problem. We wish also to broaden the wound hormone concept to include not only materials which stimulate cellular proliferation but also materials which may accelerate cellular metabolism during the healing process.

It is not our purpose to provide an exhaustive review of "wound hormones." Nor is it the intention of the authors to review the manifold aspects of wound healing. This has been done in the excellent paper of Arey.

WOUND HORMONES

Many years ago, in 1858, Virchow suggested that healing was the result of a direct stimulation of the cells by the traumatism. Wiesner appears to have been the first, in 1892, to suggest that the traumatic effect is an indirect one, the injured cells releasing substances (wound hormones) which stimulate the normal cells to proliferation. These suggestions were made with regard to plant tissues. Not until 1913 and later did the botanists Haberlandt and Reiche produce further evidence to substantiate this hypothesis. Recently a series of researches by Bonner and English has resulted in the isolation from plant tissues and subsequent synthesis of a substance which they believe to be a plant wound hormone and have accordingly named "traumatin," although no evidence has been adduced for its increased formation as a result of injury.

The application of the "wound hormone" hypothesis to animal tissues likewise suffered a severe time-lag. In 1891 Welch "presented the hypothesis that the formative stimulus of Virchow consists of substances acting from without which directly stimulate cells to growth and proliferation; the stimulating principle would be, therefore, chemical in nature" (Arey). Not until 1922 and 1924 did Naswitis present preliminary information concerning the existence of wound hormones. "Necrohormones" derived from injured tissues were studied by Lorin-Epstein and Fraenkel. Carrel, as a result of his long series of studies extending back to 1912, observed that definite growth-promoting substances are secreted by leucocytes and are present in embryonic tissue juices. He suggested (1924) that "trephones," elaborated by the leucocytes, were the primary stimulus to repair in animal wounds. Later (1930) he stated that, in superficial epithelial wounds, the reparative stimulus must consist of materials from the injured cells themselves. It was believed by Carrel and Baker that the growth activity could be attributed to split products of proteins (polypeptides) and to glutathione and hemoglobin. Many researches conducted by Hammett on both plant and animal tissues led him to the conclusion that the sulfhydryl radical is the essential stimulus for cellular proliferation and applications of this conclusion have been made to wound healing by Hammett and Reimann.

Based upon these observations, many trials of embryonic extracts, leucocytes, protein decomposition products, and tissue destruction products have been made on experimental and clinical wounds, usually with a reported lessening of healing time. References to this work are given by Arey.

It is not within the province of this paper to discuss in detail the use of many other substances which have been employed to promote wound healing, such as urea and allantoin. Although these substances occur naturally, as, for example, in the excretá of maggots, there is no evidence of which the authors are aware to link them with the "primary stimulus" to wound repair as the result of the wounding itself. Similarly, fish liver oils, although natural products, do not appear to be associated with wound repair in the manner of which we are speaking. The considerable literature on this subject is ably reviewed by Holmes who points out the lack of unanimity of opinion as to the nature of the active factor in the oils, although this has been variously identified with vitamins A and D and with fatty acids. The present case for vitamins is outlined by Hardin. Unpublished experiments on animals in our laboratories, in which were used not only fish liver oils but also fat soluble preparations from beef liver, rat liver and spleen, have led us to believe that the proliferation promoting activity, while possibly accumulating in the vitamin containing fractions,

From the Research Laboratories of the Institutum Divi Thomae.

is not attributable to the vitamin content. The experiments of McJunkin and Matsui on the epithelial regenerative activity of the fat soluble portion of rat tail scrapings seem to be in agreement with this view. Getz appears to have demonstrated that the healing effects of cod liver oil in experimental tuberculous lesions reside neither in the fatty acids nor in the vitamin A and D contents, but in an unknown factor in the unsaponifiable residue.

Nearly all of the workers with natural cellular products have regarded the materials responsible for the increase in cellular proliferation to be products of tissue destruction. In our laboratories techniques have been developed for the controlled injury of cells under reproduceable and more or less quantitative conditions, and we believe that our experiments indicate that cells subjected to injuring agents secrete or release proliferation promoting (and respiration stimulating) substances as a direct response to the injury. These factors are not solely cellular destruction products nor do they consist wholly of nutrient materials, but rather they may be hormone-like substances, in the original sense of Brown-Séquard and d'Arsonval, secreted by injured living cells into the intercellular fluid. For this reason they have been spoken of as "intercellular hormones." In our investigations (Sperti, Loofbourow, Fardon, Cook and collaborators), yeast, bacteria, algae, and animal tissues injured by controlled dosages of lethal ultraviolet radiation and x-rays as well as by chemical injury, mechanical injury or trauma, and by oxygen-want have been shown to produce factors which stimulate the proliferation of cells *in vitro* and, at least in one instance, *in vivo*. The fact that many of our studies have used yeast as a test organism does not deprive them of clinical interest, since it has been shown that, in many cases, the tissue active factors also stimulate yeast proliferation, and the latter is experimentally much better suited for quantitative assay purposes.

The evidence seems to show that injured living cells form hormone-like proliferation promoting factors as a specific response to injury although the release of dead cell disintegration products and increased permeability of the cell membrane may account for some of the activity in crude preparations.

Specific experimental results with cell suspensions which support these contentions include the following:

1. A given dosage of injuring agent, such as ultraviolet irradiation, applied at low intensities to a suspension of cells over a long period of time so that the rate of killing is low as compared with the application of the same dosage at high intensity for a shorter and more rapidly lethal period results in the formation of greater quantities of proliferation promoting substances, the yield, within limits, being closely proportional to the time required to kill the cells;

2. A comparison of the curves for the rate of killing by lethal ultraviolet with the curves representing rate of production of growth factors shows that the maximum production of proliferation factors takes place before appreciable killing occurs;

3. Application of a given dosage of injuring agent, such as ultraviolet, followed by the killing of the surviving cells by other means, as by heat or grinding, produces more potent growth promoting extracts than by reversing the process, i.e., first killing (by heat or grinding) and then applying the injuring agent;

4. Experiments on the use of various media for suspending cells during the application of injurious radiation show that nutrient or nontoxic isotonic media allow the greatest yield of the growth factors for the same dosage of injuring agent;

5. Carbon dioxide increases the yield of active factors in the intercellular fluids without killing the cells;

6. Carcinogenic hydrocarbons, such as 1,2,5, 6-dibenzanthracene, increase the yield of active factors by cell suspensions without appreciable killing of the cells.

These findings receive further, although less quantitative, support from experiments on the effects of trauma on tissues in culture. Certain of these experiments are considered in the following section.

THE BEHAVIOR OF GROWTH PROMOTING FACTORS IN TISSUE CULTURE

It has been shown directly and indirectly by several investigators that growth promoting substances are released by excised fragments of embryonic and adult tissue *in vitro*. Explanted pieces of embryonic tissue in simple saline solution show migration and cell division. Fischer (1917) holds that such cultures grow at the expense of nourishing and growth promoting substances liberated by the cells of the explant. Carrel (1913), working with cultures of connective tissue, demonstrated the remarkable power of embryonic tissue extract upon the multiplication of such cells. It was also shown by Carrel (1912) that extracts of adult spleen, leucocytes, and Rous chicken sarcoma considerably accelerated the growth of such cul-

tures. Working with cultures of adult tissue, Drew found that products of autolysis from disintegrating adult cells initiated the multiplication of such tissue and produced growth of explosive character. However, making subcultures of these in fresh media and again adding the autolyzed tissue extract, he found rapid degeneration to set in, while other cultures which did not receive a second dose of the extract continued to grow vigorously. Walton noted that if a piece of rapidly growing tissue was cut in two, growth was delayed on the cut edge (he was of the opinion that this was apparently due to trauma), so that when the cells from the uncut edges had formed a halo of branching cells spreading out into the plasma, only a few cells were projecting from the cut portion. These cells grew rapidly, however, and after the second or third day nearly equalled in width the outgrowth from the uncut edges. Walton apparently made no special issue of increased growth after injury, but was mainly interested in the lag period.

Fischer, in studying the physicochemical nature of growth promoting substances, employed various methods of obtaining embryo tissue extracts. He found (1917) that extracts obtained by simply cutting embryos into pulp with a pair of scissors gave greater activating power than when this pulp was subjected to grinding in a mortar with kieselguhr. These results suggest to us that injury rather than complete destruction of the cells produces the highest concentration of growth promoting substances. These experiments were repeated in our laboratories with the same results obtained by Fischer. Further work by Fischer (1930) on the healing of wounds *in vitro* has shown that, after successive traumatization, the cultures grew definitely faster than the undamaged controls. He observed also that the speed with which wound healing takes place in such cultures could be measured and was found to be inversely proportional to the age of the culture.

To demonstrate the liberation of growth promoting substances from injured tissue, a series of *in vitro* experiments was initiated in these laboratories. Embryonic chick heart was chosen for explantation, and plasma-Drew's solution for the medium. The tissue fragments for the control cultures were immediately transferred to hanging-drop slides. The pieces of tissue used in the experimental group were placed in a serological tube and washed thoroughly with Drew's solution by shaking gently for 30 seconds. This procedure was repeated six times with every piece of tissue, the old fluid each time being pipetted off and replaced with fresh Drew's solution. Thereafter each fragment of tissue was transferred to a slide culture and incubated with the control group which was not washed. Growth measurements were taken after an incubation period of 41 hours. The results may be summarized as follows: Twenty-four per cent of the unwashed tissues showed growth ranging from *no growth* to *poor*, while in the washed tissues 53 per cent showed either *poor* or *no growth*. Contrariwise, only 47 per cent of the washed tissues showed growth ranging from *fair* to *very good*, while 76 per cent of the unwashed tissues exhibited growth ranging from *fair* to *very good*. These results clearly indicate that washing the tissue before explantation removes much of the growth stimulating substances produced through injury by cutting, and is reflected in subsequent reduced growth.

Another series of *in vitro* experiments was performed in these laboratories to demonstrate more directly the stimulation of growth as a result of injury. To illustrate with any degree of directness that injured tissues liberate growth promoting substances entails several technical difficulties. After a fragment of tissue in a plasma clot is cut and oriented it is often difficult later to recognize the cut portion. It frequently happens—although the cut portion be recognizable—that the resultant ubiquitous migration of cells produces a pattern which gives the false impression of uniform growth from all portions of the tissue. To circumvent these difficulties a tissue was chosen in which the cut portions were easily distinguishable and relatively remote from the uncut portions. For this experiment intestine removed from 14 to 18 day old chick embryos was carefully cut into transverse sections not exceeding 2 millimeters in length. In transferring the sections to the cover slips, special precautions were taken not to injure any portion of the muscular coat of the intestinal wall. Each fragment of intestine was so oriented as to make clearly visible the two cut ends. Active growth in every instance proceeded from the cut or injured portion of the intestine sections.

In summarizing the experimental results of the *in vitro* investigations, it appears evident that growth promoting factors are liberated from tissues in culture as a consequence of injury.

METABOLISM

While considerable effort has been devoted to the stimulation of proliferation in wounds—including use not only of products of cellular injury but also of allantoin, urea, fish liver oils, sulfhydryl compounds, etc.—much less attention has been devoted to the problem of the effect of injury on

tissue metabolism. Since energy for proliferation must be supplied by metabolism, the well known fact of high metabolism of rapidly growing normal tissue, such as embryo tissue, would be expected. A similar relation holds in aseptic wounds. Gaza and Gissel, by means of the Warburg technique, measured the respiration and anaerobic glycolysis in aseptic wounds of the human skin. It was found that shortly after infliction of the wound, a rapid fall in metabolism occurs, corresponding to the destruction of tissue. When repair begins, a rise in metabolism occurs above normal, and the metabolism finally declines to the normal level. Similar findings were obtained from study of the metabolism of the Achilles tendon of the dog. It has been pointed out that respiration may be lowered in a number of pathological conditions or by toxic agents and that its measurement may serve as a criterion of the vitality of the skin and, for that reason, may be a useful adjunct in dermatology (Adams, Amersbach and associates, Cook).

In our laboratories the effects of injuring agents such as ultraviolet and x-radiations, on the respiration of cell suspensions have been studied, conditions similar to those employed in the proliferation investigations being used. It was found that mild irradiation caused an increase in respiration while intensive irradiation, with resulting destruction of most of the cells, caused a decrease or cessation of respiration (Fardon and associates, 1937). It was shown that such irradiation caused the release by the injured cells of a factor (or factors) which could be separated from the cells and which was active in increasing the respiration of fresh cell suspensions. Thus, it appears that cells, under the influence of injuring agents, release into the intercellular fluids substances which stimulate the proliferation and respiration (and also, less extensively investigated, the glycolysis) of cells. Effort is being expended on the preparation, fractionation, and characterization of these substances and their relation to other recognized materials (Cook, Norris, and collaborators). As a result of these studies we believe that the injury of cells causes them to release (and probably to synthesize in increased quantities) not only chemicals which induce more rapid proliferation but also chemicals which tend to restore the metabolism which has been lowered as a direct result of tissue destruction. Present indications are that the growth and respiratory stimulating factors are distinct; and, at least under our experimental conditions, relatively greater proportions of the growth factors are produced by injury.

NATURE OF RESPIRATORY PROMOTING AND PROLIFERATION PROMOTING FACTORS

1. Respiration promoting factors. Little is known as yet of the chemical nature of the respiratory factors with which we have been dealing and consequently we are unable to state how these factors may fit in with the recognized respiratory systems and to just what extent they may be identical with known respiratory intermediaries. Our efforts in connection with both the respiratory and proliferation factors have, until recently, been directed primarily toward the physiological aspects of the problem, i.e., the effect of injury on the production of these materials, and less toward their nature and mode of action. Certain indications are available, however (Cook and associates). In crude extracts undoubtedly mixtures containing both coenzyme-like substances and oxidative substrates are present. There is evidence that a variety of materials, more or less specific as to tissue, are involved. It has been possible to eliminate a variety of amino acids, members of the vitamin B complex (thiamin, riboflavin, nicotinic acid, pyridoxin, pantothenic acid) and other substances as major sources of activity on yeast respiration (Cook, Walter and Eilert, 1940) as well as on skin respiration (unpublished) under our experimental conditions. The active materials appear to be free of protein and sulfur, and all the active water-soluble preparations thus far obtained contain nitrogen. A material active in increasing liver respiration has been concentrated by fractional electrical transport and is definitely acidic in nature. Certain of the common participants in cellular oxidation systems, such as the thiamin containing and alloxazine containing coenzymes and coenzymes I and II, appear to be eliminated by the lack of correlation between ultraviolet absorption and respiratory activity. Certain fatty substances which, in nontoxic concentrations, increase the respiration of yeast have been shown to be fatty acids acting as substrates.

2. Proliferation promoting substances. It was early established that there was a correlation between the proliferation promoting capacity and the amount of ultraviolet absorption at approximately 2600 Ångstroms in the crude concentrates of proliferation promoting factors from both yeast and animal tissues (Loofbourow, Cook). This was taken as evidence of a nucleic acid-like nature of the proliferants. Recently, however, experiments have shown that, while an increase in nucleic acid (or similar substances) can be demonstrated in ultraviolet injured cells either directly (by the quartz microscopic technique) or by isolation, and

while a parallel increase in growth potency also takes place (Loofbourow et al., 1941), yet it is possible by the technique of chromatographic adsorption to obtain potent extracts which do not show selective ultraviolet absorption. No correlation was observed between ultraviolet absorption at 2600 Ångstroms and growth potency of fractions from "uninjured" cells (Cook, Hart, and Stimson, 1940). Davidson confirmed the growth promoting properties and the increased content of purine, nucleotide, and nucleoside nitrogen in the cell free fluids from ultraviolet injured yeast cells and also found a large increase in amino nitrogen. It may be recalled that Caspersson has demonstrated an increase in nucleic acid during cellular division and Fischer (1939, 1940) believes that a nucleoprotein is responsible for the proliferation effects observed by him and previously referred to in this paper. A preparation from beef embryos based on Fischer's work and known as epicutan is being investigated in the healing of war wounds in England.

A series of unpublished experiments comparing cell free extracts from ultraviolet irradiated yeast with the known growth factors for yeast (inositol, thiamin, biotin, vitamin B_6, pantothenic acid and amino acids) has shown that, while part of the activity of crude extracts is accounted for by certain of these substances, there is yet a residual effect due to substances not yet recognized. This is confirmed by work of Williams and associates.

Injury, therefore, would appear to result in the release of proliferation promoting substances, some of which represent an increased production of known materials, but some of which are yet unknown. It may be mentioned that no evidence has been found to relate these materials to the sulfhydryl compounds of Hammett since none of them contain sulfur.

SUMMARY

Evidence is presented that living cells, upon injury, produce or release substances which promote the proliferation and metabolism of surviving cells. While crude preparations from injured cells contain cellular disintegration products which can serve as nutrients, it is believed that injured cells secrete into the intercellular fluid additional materials which may be hormone-like in their action, in the original sense of Brown-Séquard and d'Arsonval, and which, therefore, may be termed "intercellular hormones." It is believed that these substances are of importance in wound healing and may constitute the "formative stimulus" of Virchow. The efficacy of such contemporary modes of therapy as the Orr treatment may be due in part to the retention of such substances at the wound site. The work reported herein is being extended to *in vivo* studies of animal and human wounds and will be reported later.

(A full bibliography will be included in the reprints.)

A SIMPLIFIED TECHNIQUE FOR THIGH AMPUTATION

PHIL THOREK, M.D., F.A.C.S., Chicago, Illinois

ONE hesitates to write an article on a so called "new technique" for thigh amputation. So many operations have been devised that it is difficult to imagine another new procedure. The procedure herein described, however, is the result of operations previously described and so modified that a simple effective technique has resulted.

This series comprises 40 low thigh amputations performed by the method to be presented. Our results have been good and the mortality respectably low. In the 40 cases there were 3 deaths, none of which occurred immediately following operation. Twenty of these amputations were done by the author, and the remaining 20 by two surgical residents at Cook County Hospital (Drs. J. W. Howser and W. N. Knudsen). By paying strict attention to a few details and by carrying out the procedure in a step by step manner, the routine developed has resulted in a rather simplified amputation.

Eliason and Wright, McKittrick and Root, Callander, and Samuels have contributed much to this subject, especially in the diabetic patient. Their experiences tend to show that a supracondylar type of amputation, even in the presence of infection, should be a relatively simple operation and should not result in a high mortality. All of these authors emphasize the importance of good preoperative and postoperative care.

While generally accepted that spinal anesthesia is the anesthetic of choice in the aged and in the diabetic, Samuels has reported excellent results with cyclopropane or nitrous oxide. He states that since spinal anesthesia has a tendency to diminish the blood flow in the extremities, this may be looked upon as a contraindication for its use in amputations. He has suggested that this may play a rôle in thrombosis in the arteries of the opposite extremity. In our series of 40 cases, 20 patients were anesthetized by cyclopropane and 20 with nitrous oxide. Ether has been abandoned. We believe that cyclopropane is the anesthetic of first choice. In the absence of cyclopropane, our second choice is ethylene. The immediate postoperative course in these patients has been most gratifying.

The draping of the patient, which at first thought appears to be an indifferent step, should be done by the surgeon himself. The draping should be done in such a way that the second assistant may execute internal rotation, external rotation, or elevation of the leg at any time without hindrance to motion and without danger of contamination.

The technique about to be described is different in that flap formation is considered unnecessary, no tourniquet is used, drains have been abandoned, and cotton is used for suture material instead of catgut.

The position of the surgeon at the operating table is important. He should occupy a position opposite the leg which is to be amputated. The reason for this is that since no tourniquet is applied he should have ready access to the popliteal vessels. These vessels may be approached easily through the medial aspect of the popliteal space. To attempt a lateral approach to the popliteal vessels is both cumbersome and difficult. The first assistant stands directly opposite the surgeon. The second assistant is at the foot end of the table, manipulating the leg into any position which the surgeon might desire. After a surgical team has gone over the procedure a few times, these manipulations become automatic.

The skin incision is so placed as to permit amputation at the lower third of the thigh. This is the generally accepted site of choice. The incision is made with a new, sharp scalpel blade. Since tissues, especially tissues of lower resistance are readily traumatized by dull blades, we prefer to use a medium-sized detachable blade. With the leg fully extended, the surgeon feels the upper border of the patella, and at this point makes a simple circular incision (Fig. 1, a). It has been a great source of relief to us to find that this simple circular incision allows the flaps to fall together and heal better than do other incisions previously used by us. This incision includes skin and superficial fascia. Over the medial side of the incision, the internal saphenous vein is identified, ligated, and severed. It is recalled that this vein runs in the superficial fascia and on the fascia lata. We utilize this vein as a guide to the sartorius muscle. There is no undermining or undercutting of any tissues.

The incision having been completed, a fresh scalpel blade is taken and a similar incision is made in the deep fascia. Our attention is now directed to the four muscles which lie medial to

From the Department of Surgery, University of Illinois, Cook County Hospital.

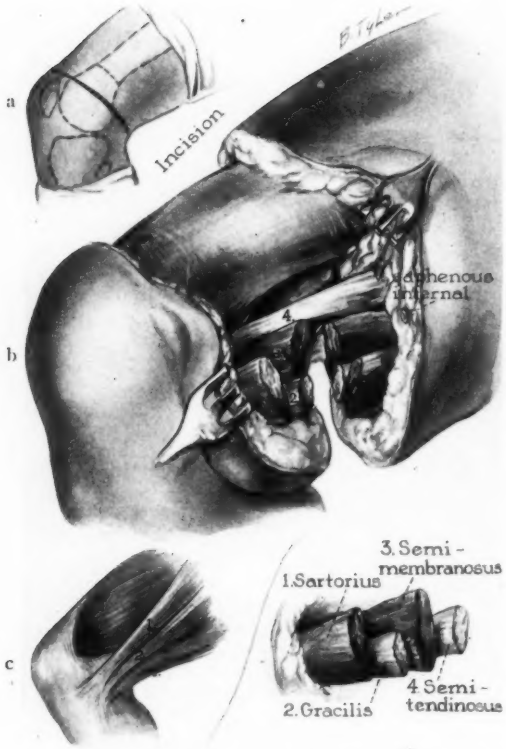

Fig. 1. a, Suprapatellar circular incision. b, Simplified division of medial musculature; semitendinosus intact. c, Anatomy of medial musculature.

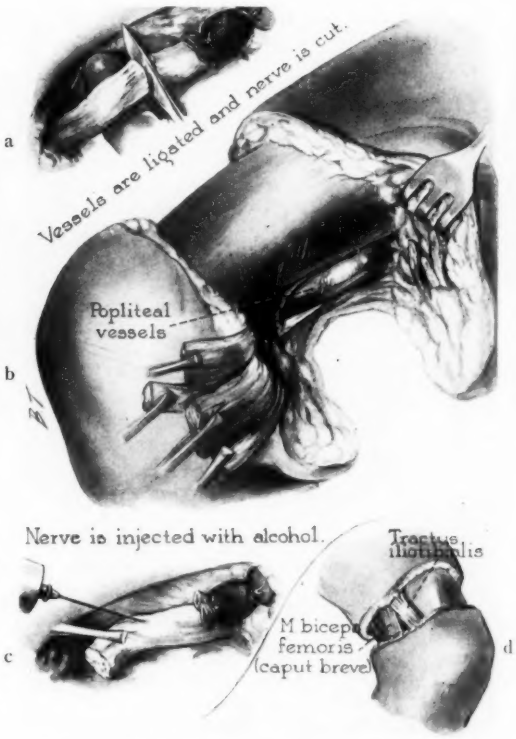

Fig. 2. a, Isolation of popliteal vessels. b, Division of sciatic nerve. c, Traction on nerve and injection of alcohol. d, Anatomy of lateral musculature.

the popliteal spaces. These are: the sartorius, gracilis, semimembranosus, and semitendinosus (named from superficial to deep) (Fig. 1, b and c). They are easily identified and separated from each other. They do not require ligation since no large vessels run through them. Two of these four muscles, the sartorius and the semimembranosus, are muscular in this region; the remaining two, the gracilis and semitendinosus, are tendinous. We have noticed no ill effects as a result of cutting through the muscle. From the standpoint of infection, particularly the gas bacillus type, the importance of a sharp scalpel and the avoidance of crushing these structures with ligatures or hemostats cannot be overemphasized. In our series we have not seen a single case of gas gangrene.

Following the division of the four medial muscles, the next step is the isolation, ligation, and division of the popliteal vessels. This step becomes simple if the following maneuver is executed. The index finger of the right hand is placed against the posterior aspect of the femur. The bone should actually be felt. This finger is then thrust laterally, hugging the posterior surface of the femur all the way. Having done this, the popliteal artery and vein may now be hooked by the index finger and delivered medially. The popliteal space is filled with a peculiar watery type of fat. Some of this fat clings to the vascular bundle. There is no difficulty, however, in feeling the pulsations of the popliteal artery through this fat. This liquid fat is easily wiped off of the vessels by means of a moist gauze sponge. The vessels now stand out in bold relief, especially the artery, the pulsations of which are distinctly visible. No attempt is made to separate the artery from the vein (Fig. 2, b).

The vessels are ligated with No. 24 cotton ligatures which have been doubled. Two ligatures

are placed proximally around the artery and vein, tied and cut short. A double ligature is placed around the distal aspect of the vessels. This distal ligature is placed only to prevent regurgitant venous bleeding. A hemostat may be used in its place. We have found, however, that such a hemostat dangling in the wound obscures the field. The vessels are now severed between the distal two ligatures. The atheromatous condition of the vessels are usually seen at this stage of the operation.

The sciatic nerve should now be carefully dissected out and brought up with a wet tape. Some authors prefer to refer to the nerve as the popliteal in this locality. Since the operation is performed above the popliteal space, the term sciatic is more appropriate. The nerve is delivered to the medial surface of the thigh, caught with a toothless, nontraumatizing forceps, severed, injected with 1 cubic centimeter of absolute alcohol and ligated with a single cotton suture. In some of these cases we have intentionally omitted the injection of alcohol into the nerve. These patients complained of a greater amount of postoperative pain. Such pain lasted about a week. Based upon this experience, we consider the injection of the nerve essential. This also for the purpose of preventing the development of amputation neuroma (Fig. 2, a and c).

The second assistant is instructed to rotate the leg and thigh medially. This brings the two lateral structures which are to be divided, into view. These are the tendon of the biceps femoris and the iliotibial band (Fig. 2, d). The biceps tendon is the most dorsal structure in this region. It can easily be followed to the head of the fibula if one is not sure of its identity. This tendon is divided. The iliotibial band runs a full finger's breadth in front of the now divided biceps tendon. It too is severed.

Having detached the medial, lateral, and posterior structures, this leaves only the anterior muscle mass, the quadriceps femoris muscle, to be divided. Immediately posterior to its medial border the adductor magnus tendon is found. This entire mass is cut through at that level to which the skin has retracted. The incision through the muscle mass is carried down to the bone. No retraction of the muscle is necessary since it retracts by itself. The periosteum is incised with a circular sweep around the femur. The periosteum is then elevated proximally and distally with a periosteal elevator (Fig. 3, a).

It is now noticed that the soft tissues fall away from the femur, but remain attached at only one point. This point is posterior where the muscles

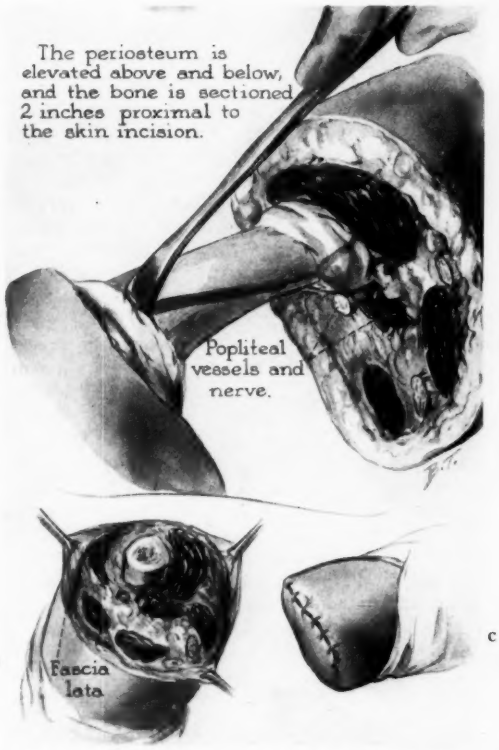
The periosteum is elevated above and below, and the bone is sectioned 2 inches proximal to the skin incision.
a
Popliteal vessels and nerve.
b
Fascia lata
c

Fig. 3. a, Elevation of periosteum following division of sciatic nerve. The nerve retracts. The edge of the nerve is depicted in the figure for anatomical orientation. b, The fascia lata is identified and grasped with Allis forceps. c, Closure with interrupted sutures.

are attached to the linea aspera. If a few light strokes are made with the scalpel along this posterior attachment to the linea aspera, the entire soft tissue mass falls away from the femur and can now easily be retracted upward (proximally).

If the bone is sawed through, 2 or 3 inches above the level of the skin incision, an excellent stump results. We have no difficulty with protruding bone or pressure necrosis from the underlying bone. The bone can be removed high enough, only if the attachments to the linea aspera are detached posteriorly. This point cannot be overemphasized. Some surgeons insist that curetting of the bone is essential. We have avoided it.

The leg being amputated, the second assistant is now free to hold the stump. He holds the stump in such a way as to permit its cut surface

to face directly upward (Fig. 3, b). The fascia lata is easily identified as a strong layer completely encircling the thigh and surrounding the muscles, vessels, and nerves. This layer is picked up with Allis forceps and sutured, transversely, with a few interrupted cotton sutures. The muscles are not sutured together. The approximation of the fascia lata guides the muscles over the end of the bone so that the cut muscle surfaces touch each other. In this way no dead spaces result, and no sutures are placed in the muscles.

All that remains now is to approximate the skin edges. The ease with which this is accomplished is gratifying. It is surprising to find that although no flaps have been fashioned, two well approximated flaps result. At each corner two small skin tabs, "dog ears," result. These may either be trimmed off or left alone. We prefer the latter since we have found that the skin at the edges of the wound shrinks and retracts by itself.

The resulting scar is at the end of the stump. This may be criticized by some as producing a painful weight-bearing stump. This may not be a valid criticism since the artificial limb of today does not apply pressure to the end of the stump alone. Instead, the pressure is applied in "bucket fashion" to the sides of the extremity and to bony prominences, as the ischial tuberosities as well as the end of the bone. This, however, is still a moot question.

A light dressing is applied and is held in place by adhesive tape which is not applied too tightly. Circular bandages have been abandoned because they have a tendency to constrict and interfere with an already impaired circulation. No splint or traction apparatus is applied.

These patients are told to move their stumps as early as possible. An attempt is made to have them out of bed on the second or third postoperative day. This is not always possible but is the rule in the majority of cases. Diabetics are immediately returned to their diet-insulin regimens. Every other suture is removed on the fifth or sixth postoperative day and, if there is no gaping, the remaining sutures are removed on the following day.

In none of these 40 cases were drains used. To drain or not to drain these stumps is still a moot question. We have adhered to the teaching that a drain acts as a foreign body, thereby causing drainage, delays healing, and encourages infection.

Cotton sutures (4) have been used throughout the entire procedure because it does not produce draining sinuses and because it results in a smoother and simpler operating technique.

CONCLUSIONS

1. A technique for thigh amputation has been described.
2. The importance of no flap formation and the omission of the use of the tourniquet has been stressed.
3. Drains in these postoperative wounds have been discontinued.
4. The possible disadvantages of spinal anesthesia in these cases have been pointed out.
5. Cotton was used as the suture material.

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HABITUAL DISLOCATION OF THE SHOULDER JOINT

S. L. ODGERS, M.D., and F. W. HARK, M.D., Chicago, Illinois

RECURRENT dislocations of the shoulder joint have been recognized for centuries, Hippocrates being credited with the first description. However, as in many other lesions, treatment has not kept pace with clinical recognition. This, of course, is due either to (1) lack of full understanding of the lesion, (2) paucity of therapeutic measures, or (3) inability of the body to repair itself.

Centuries ago the ailment was treated by plunging a hot iron into the axilla. It is hard to say how many cures were derived from this very radical procedure. No real rationale can be attached to the method as far as the operators were concerned, since microscopic anatomy of repair as well as of gross lesions were poorly understood.

In 1870 Theodore Kocher, of Berne, described his manipulative principles of reducing anterior dislocation of the shoulder. These principles, although condemned by some, are still in modern textbooks. In 1882, Cramer and others practiced resection of the humeral head for this condition. By 1888 Albert was advocating arthrodesis of the shoulder joint. Ricord, in 1894, was one of the first to do a capsulorrhaphy. Hildebrand attempted to deepen the glenoid fossa in 1902. In 1903 C. Beck plicated the capsule and threaded silver wires through the acromion process and head of the humerus. Five weeks later the wires were removed. Six months later the result was still good.

By 1909 Clairmont and Ehrlich detached a part of the posterior deltoid, passed it beneath the subcapital portion of the humerus and reattached the muscle flap to the muscle body anteriorly. In 1917 Clairmont strengthened the coracoclavicular ligament. This same year, Joseph gave the technique of tenosuspension by placing drill holes through the acromion and tuberosity of the humerus. In his method, fascia lata was used as the suspending material.

M. Henderson devised a similar operation in 1921, but used the peroneus longus tendon instead. His article of that time states "that dislocation of the shoulder is not more common demonstrates how wonderful are the mechanism and muscle balance that prevent such an occurrence." In further support he says, "I am convinced that some altered muscle tension has to do with the production of the dislocation. This muscle tone may be caused by an alteration in the relationship of muscle to its original insertion; for example, it has been claimed by many that the relationship of the supraspinatus and infraspinatus to their insertion is altered by their being partially torn off at the time of the original injury."

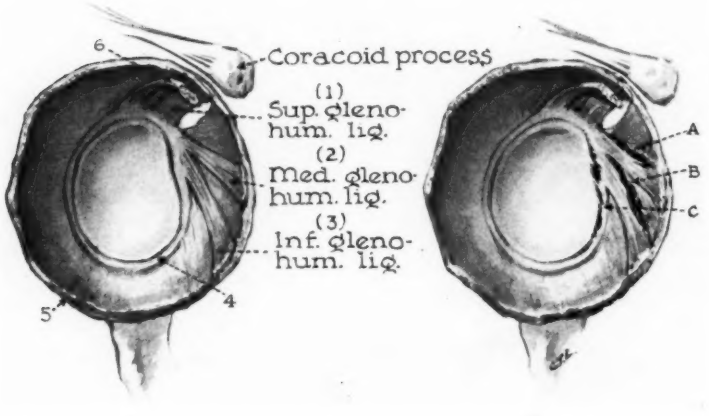
In an article written in 1926 Henderson states that, in recurring dislocation of the shoulder, the head of the humerus is practically always downward and forward. There is no mention of disturbed muscle relationship. In his series capsulorrhaphy gave 42 per cent cures after 5 years. However, Henderson believed that tenosuspension was better.

Carrell, in 1927, was using the long head of the biceps brachii for the repair of recurrent dislocations. In Carrell's own words, "The biceps tendon was sectioned at the lowest level and reflected from its sheath up to the point where it emerges from the capsule. The distal end was fashioned into the coracoid head of the biceps. A strip of fascia 6 or 7 inches long and 1.5 inches wide was securely fastened to the free end of the biceps tendon. A posterior incision was then made, extending from the acromion downward on the posterior surface of the arm 4 inches. The deltoid was separated and the teres minor exposed. The biceps and fascial strip was now passed under the neck penetrating the capsule, in and out at two points; it was then threaded on a special instrument fashioned like an aneurysm needle. The instrument hugs the capsule and emerges just above the teres minor, where it is secured through a drill hole in the acromion." Carrell states that this method is good for any type of dislocation.

Nicola in 1929 presented, "A new operation," for the repair of recurrent anterior dislocation of the shoulder. He uses the long head of the biceps brachii and threads it through the head of the humerus. Nicola argues that this operation can be used when the pathological condition is due to bony, muscular, or capsular defects or to any combination of these defects.

In 1938 Bankart published an article entitled, "The Pathology and Treatment of Recurrent Dislocation of the Shoulder Joint," in which he stresses that recurrent dislocation is not the ordi-

From the University of Illinois College of Medicine.



a b

Fig. 1a. Looking into the shoulder joint after removal of the head of the humerus from its end of the capsular tube; *5* is the free margin of the capsular tube; *4* is the end attached to the rim of the glenoid which contains the thickened triangular fibrocartilaginous band known as the glenoid ligament. *1*, *2*, and *3* represent the artist's idea of the thickenings in the capsule known as superior, middle and inferior glenohumeral ligaments; *6*, intra-articular biceps tendon. b, *C*, Tear between rim of the glenoid rim and the glenoid ligament, *4*. *B*, Rent between the middle and inferior glenohumeral ligaments. *A*, Rent humeralward from the middle glenohumeral ligament.

nary sequel of ordinary traumatic dislocation. That is to say, ordinary dislocation is due to a fall on the abducted or outstretched arm and by deflection against the acromion, the head is forced downward through the capsule and between the subscapularis and triceps muscles. These heal after the dislocation is reduced.

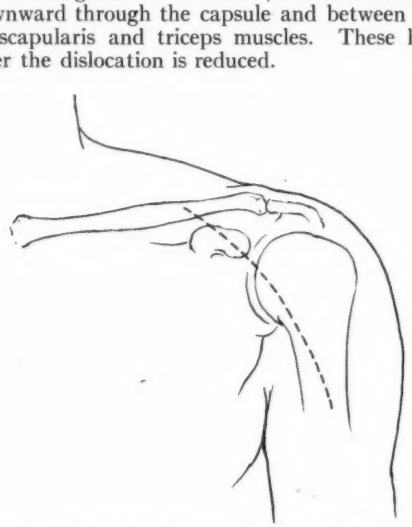


Fig. 2. The incision begins at the clavicle, crosses the coracoid process and is directed toward the external epicondyle which is the course of the cephalic vein.

The recurrent type, however, is due to a direct force on the shoulder from behind on the elbow when the latter is directed backward. In this injury then, to quote Bankart, "The head of the humerus is forced out of the joint, not by leverage, but by a direct drive from behind forward. In its passage forward the head shears off the fibrous or fibrocartilaginous ligament from the attachment to the bone. The detachment occurs over practically the whole anterior half of the glenoid margin. The reason why the dislocation recurs after reduction is that, whereas a rent in the fibrous capsule heals readily and soundly, there is no tendency whatever for the detached glenoid ligament to reattach itself to the bone. The defect in the joint is, therefore, permanent, and the head of the humerus is free to move forward over the anterior margin of the glenoid cavity on the slightest provocation."

THE ANATOMY

The shoulder joint is a ball and socket joint. In order that the range of motion might be great, the glenoid fossa is quite small as compared with the head of the humerus. Consequently, stability depends upon the muscular and capsular structures about the joint. Someone has remarked that the capsule is lax and thin and is inconsequential as far as stability of the shoulder joint is

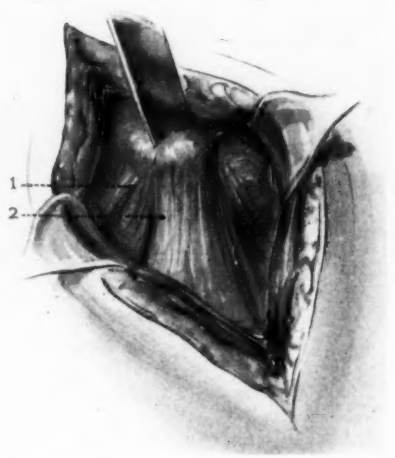


Fig. 3. Chiseling free the tip of the coracoid containing the pectoralis minor, *1*, and biceps and coracobrachialis.

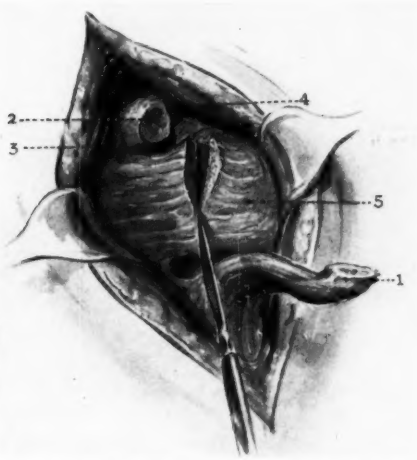


Fig. 4. Cutting the subscapularis, *5*, not too close to its insertion into the capsule and humerus. *1*, Reflected tip of coracoid with biceps and coracobrachialis; *2*, stump of coracoid process; *3*, pectoralis muscle; *4*, deltoid muscle.

concerned. Our present interest centers in that part of the capsule anterior to the shoulder joint. Slightly below the coracoid process is an opening which is the foramen allowing communication between the shoulder joint and subcoracoid bursa. Occasionally this foramen is beneath the uppermost fibers of the subscapularis. In order more thoroughly to examine the capsule let us enucleate the humerus from its end of the capsular tube (Fig. 1a).

On inspection one does not notice anything unusual about the capsule but upon taking it between the thumb and index finger two areas of thickening can be felt. These bands begin near the upper border of the glenoid and run forward and downward toward the humerus. The upper is known as the middle glenohumeral ligament (Fig. 1a, *2*), and the lower as the inferior glenohumeral ligament. There is yet a third which, because of its location, cannot be so readily palpated. It is the superior glenohumeral ligament. It begins at the upper margin of the glenoid, bifurcates to pass around the origin of the long head of the biceps tendon, and continues to the neck of the humerus superiorly (Fig. 1a, *1*). It lies directly under the coracohumeral ligament and should not be confused with it.

On inspecting the inside of this capsular tube, one notices at its base the glenoid fossa and about its periphery where it joins the capsule, there is a raised fibrocartilaginous band known as the labrum glenoidale or glenoid ligament (Fig. 1a, *4*). Cunningham states that it is within the fibrous capsule and attaches to the margin of the glenoid cavity, and that to some slight extent it increases the security of the articulation.

In the dissecting room we examined about 40 shoulders and found 6 instances of tears in the anterior capsule of the shoulder joint. Three tears were between the bony glenoid margin and the glenoid ligament (Fig. 1b, *c*). Two presented a rent between the glenoid rim and the glenoid ligament, and a second tear between the inferior

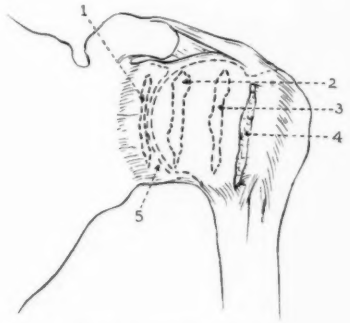


Fig. 5. The artist's conception of the tears as viewed extracapsularly in the depth of the wound. The most frequent one is in position *2*. Not infrequently the middle glenohumeral ligament traverses this rent, instead of being torn with the capsule. *1*, The site of the tear at the glenoid rim, the glenoid ligament going with the capsule. Technically this is the most difficult to repair as there is nothing to sew to except the bony glenoid rim, *5*.

Fig. 6. Placing the sutures in the tear which may traverse the middle glenohumeral ligament or lie between it and the inferior glenohumeral ligament. Bankart nicely illustrates placing the sutures in a marginal tear.

Fig. 7. Resuturing the coracoid process.

and middle glenohumeral ligament (Fig. 1b, *C* and *B*). There was one instance in which the tear was between the middle and inferior glenohumeral ligament (Fig. 1b, *B*). Grossly these tears presented some of the signs of degeneration. Two of the tears were in the same cadaver which appeared to be the body of a 70 year old individual. The capsule was not only torn away from the bony margin but there was also a rent between the glenoid ligament and the middle glenohumeral ligament, leaving the glenoid ligament free. This was worn quite ragged and thin at its upper end. In fact one was worn through, and the loose end lay in the joint in a manner similar to that in which the semilunar cartilage lies in the knee joint as a complete bucket handle tear. This same body showed extensive degenerative changes in the intervertebral discs of the lumbar spine. Other specimens showed evidence of fraying, but the state of the tissues suggested that the lesion was of many years' standing. One specimen presented a worn away capsule with the middle glenohumeral ligament and glenoid ligament floating free in space. The question arises as to whether these lesions are the result of the degenerative changes or the result of incomplete repairs which occurred many years ago. They may be both, but one would be inclined to believe the latter explanation, as the histories of our operative cases and of habitual dislocations not operated upon date from as early as the late teens and twenties.

CLINICAL MATERIAL[1]

The clinical material consists of 11 males and 1 female. Of the males, 8 injuries occurred in football games, 1 at play, 1 in a scuffle, and 1 while under metrazol treatment. The girl received her first dislocation while wrestling at a picnic. These patients were all exerting themselves, were thrown to the ground in a moment of strenuous action, when all muscles were tense and the arms close to the side of the body. They were too preoccupied to throw their arms out to catch themselves. They fall into the group where the dislocating force is applied directly to the shoulder.

Although in our Henderson tendosuspension cases, there were recurrences within 6 months in 2 cases, in our Bankart series of 12, there have been no recurrences.

At first glance the operation appears difficult. After one becomes familiar with the steps in the technique and with a well trained team, it is no more difficult than the Loefler-Henderson or the Nicola operation.

The approach is not unlike the anterior approach to the shoulder joint except that the upper end extends up to the clavicle (Fig. 2). The first landmark is the cephalic vein, which marks the plane between the pectoralis major and the deltoid muscles. After separating these two muscles, one exposes the coracoid process to which are attached the pectoralis minor, the coracobrachia-

[1]This series of cases is from the orthopedic service of Henry B. Thomas, Research & Educational Hospital, Illinois Surgical Institute for Children and St. Luke's Hospital, including one each of Claude Lambert and Fred Hark.

lis and the short head of the biceps (Fig. 3). With a little blunt dissection these muscles are clearly defined. It usually is necessary to cut the acromiothoracic artery in the upper part of the wound.

The distal ½ inch of the coracoid process with the three attached muscles is chiseled free and retracted to the lower end of the wound. The arm is turned into a moderate amount of outward rotation, and, with a few strokes of blunt dissection, the subscapularis tendon comes into view.

The brachial plexus, artery, and veins are under cover of the pectoralis major and come into view at this time if the muscle is lifted a trifle. The retractor on this side should be covered with a sponge for the protection of these structures.

The subscapularis tendon is next divided near its insertion into the capsule on the head of the humerus (Fig. 4). The section should not be too close to the capsule so that part of the tendinous insertion may be employed to reconstruct a glenohumeral ligament if the anatomical structures should be badly frayed. The operator should exercise care when sectioning the distal part of the tendon so as not to injure the axillary nerve and vessels. It will be recalled that they swing around the neck of the humerus through the quadrilateral space to supply the deltoid muscle and other posterior structures.

The capsule of the shoulder joint is now exposed and also the rent. If the tear in the capsule is small and especially if it is humeralward to the middle glenohumeral ligament, one might mistake it for the foramen between the shoulder joint and the coracoid bursa and continue to search for a further pathological process. It must be remembered that the coracohumeral foramen is directly under the coracoid process. Not infrequently the rent extends up into the foramen. Bankart remarks that the fibrous rim (labrum glenoidale) is invariably torn from the bony rim of the glenoid. Only 3 of our cases presented this picture (*C* in Figs. 1b and 5), 2 were torn humeralward (*A* in Figs. 1b and 5) to the middle glenohumeral ligament, and the rest between the inferior and the middle glenohumeral ligament (*B* in Figs. 1b and 5).

Repair is effected with 4 silk sutures placed across the rent after its edges are freshened with a scalpel. If the glenoid ligament is torn away from the glenoid margin the capsule must be sutured into bone. Bankart and others report making tunnels in bone with a heavy towel clip. Because of the depth of the wound we have used to better advantage a fine dental chisel or a chisel fashioned like an ice pick with the end slightly bent. Before the sutures are placed, the glenoid lip should be roughened so that the capsule will become more firmly adherent. In the cases in which the glenoid ligament was intact we have dispensed with placing the sutures into the bone. A suture into the glenoid ligament is quite firm. More recently we have reinforced the repair by suturing part of the subscapularis tendon across the rent particularly in the tears humeralward to the middle glenohumeral ligament. If longer fibers are desired a few tendon strands may be taken from the biceps or coracobrachialis tendon.

The subscapularis is resutured with silk or catgut. The base of the coracoid is drilled and its tip is sutured back in place with a braided silk. The deltoid and pectoralis major fall into apposition with each other. The subcutaneous tissues and skin are closed according to one's own technique, and the arm is put up in a Velpeau dressing for 1 or 2 weeks. The arm may then be carried in a sling to complete a month. There should be no abduction or outward rotation. The patient is free to use his elbow and may moderately forward flex the arm. One of our patients was back playing football 2 months after operation. All our patients have 10 to 15 degrees of limitation of outward rotation. This was still present in the 2½ and 3 year old cases. None of the patients has noted any handicap because of it.

An abstract of the first 7 cases follows: We are reporting 7 of the 12.

CASE 1. E. M., aged 28 years, injured his left shoulder 3 years ago during play. Since that time it has been out 12 or more times but he reduces it by abduction and anterior flexion of the arm. The dislocation occurs when he elevates his arm and reaches backward. Patient was operated upon November 17, 1938. There was a rent in the capsule through which the head would dislocate easily. The capsule and glenoid ligament were reattached to the bone When last seen on January 14, 1941, he had had no dislocations since repair. There was slight limitation of external rotation and hyperextension of the arm.

CASE 2. L. S., aged 19 years, injured his right shoulder in June, 1938, while playing football. After the injury he reduced the shoulder himself and wore a sling for 2 weeks. His shoulder dislocated again in the fall of 1938 and has dislocated 15 times since. In fact it was easily dislocated upon dispensary examination. He was operated upon on August 22, 1940. The capsule showed a 2 centimeter defect in the anteroinferior region with a delicate pannus growing over the glenoid rim. In the repair the capsule was freed along the glenoid rim and used for imbrication. When the patient was last seen on February 21, 1941, he had slight limitation of external rotation (5 degrees) and limitation of 10 degrees of abduction.

CASE 3. G. McC., aged 21 years, injured his left shoulder in September, 1940. This was done in a football game when he tackled an opponent and was thrown into a spin. He had no special treatment and since that time until operation it had dislocated 7 to 10 times. Any slight trauma from behind when arm was outstretched caused a disloca-

tion. The patient was operated upon on February 4, 1941. At operation the capsule showed a 1½ inch tear with a ½ inch flap still attached to the glenoid margin. This flap was roughened and the capsule was sewed directly into it. The postoperative course since then has been uneventful.

CASE 4. G. K., aged 20 years, injured shoulder 2 years ago in a football game when several players fell in a huddle. His arm was treated by strapping to his side for 2 weeks. Since then it has been dislocated several times especially when held in abduction or hyperextension. The patient was operated upon on January 4, 1941; at operation the capsule showed a 2 inch tear about ½ inch from the glenoid margin. The capsule was sewed into this flap. The postoperative course has been uneventful.

CASE 5. J. J., age 27 years. In May of 1938 the patient suffered an anterior dislocation of the shoulder while under a metrazol treatment. From that time until June, 1939, the shoulder dislocated 12 times. Each time the arm was more easily dislocated and reduced. Patient was operated upon on July 3, 1939. A considerable portion of the capsule was destroyed. The capsule was sewed into the glenoid with braided silk. The postoperative course was uneventful. When he was last seen in September, 1939, the only disability was slight limitation of abduction and outward rotation.

CASE 6. C. P., aged 20 years. In the fall of 1938, the patient dislocated his left shoulder while playing football. It was reduced by a doctor but he had no immobilization. Since then it has dislocated about 15 times. The last time it dislocated was in the winter of 1939–1940 during a basketball game. On August 19, 1940, the patient was operated upon. There was a rent in the capsule 1½ inches long. The capsule was sutured into the glenoid rim. Postoperative course was uneventful. On December 4, 1940, the patient had a good range of motion excepting slight decrease in external rotation. He is now able to play basketball without trouble.

CASE 7. M. L., 1½ years ago dislocated the left shoulder while in a scuffle. At the time the arm was reduced by a doctor. Since then he has dislocated the arm several times, once when he was asleep. On March 3, 1941, the patient was operated upon. A 2 inch tear was seen in the capsule. A slight amount of granulation tissue was seen. The capsule was imbricated with silk sutures. The postoperative course was good.

SUMMARY

Tears in the capsule of the shoulder joint under the subscapularis can be demonstrated in the dissecting room. Their location varies slightly, some being between the middle and inferior glenohumeral ligament, some between the glenoid ligament and the rim of the glenoid fossa, a few being humeralward to the inferior glenoid ligament. This pathological picture is consistently found in the so called direct force dislocation of the shoulder joint which is the forerunner of the habitually dislocating shoulder. Repair of this rent has seemed to be a proper indication as treatment for preventing subsequent dislocations.

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DIAGNOSIS AND TREATMENT OF AMEBIC LIVER ABSCESS

CLARENCE J. BERNE, M.D., F.A.C.S., Los Angeles, California

AMEBIC infestation of the liver presents important diagnostic and therapeutic peculiarities requiring full recognition if acceptable results are to be obtained. In many surgeons there is still a strong tendency to apply to this disease the principles used in controlling pyogenic processes of bacterial origin because of the frequent similarity in gross features. That such methods are exceedingly inadequate was apparent when it was found in 1931 that the mortality in this disease at the Los Angeles County Hospital was 85 per cent. Significantly, this included a high percentage of cases detected by necropsy and emphasizes that the disease is capable of such protean manifestations that much vigilance is required to secure sufficient diagnostic accuracy to make treatment effective. Since 1931, 74 cases of amebic abscess have been recognized and furnish the basis for this report, in which the diagnostic and therapeutic problems are considered.

DIAGNOSIS

Certain general features of the disease require emphasis. Amebic infection of the colon always antedates the liver lesion, but many cases of amebic colitis are clinically silent, and the usually conceived picture of amebic dysentery does not exist. Thirty of our cases gave a history of diarrhea and 44 failed to recall diarrhea, while 6 complained of constipation. Therefore in less than half the cases is a diarrhea present to suggest consideration of amebiasis. Gross colon lesions were present in 14 of the 24 cases in which portmortem examinations were made, and in 5 of these there had been no diarrhea. The foregoing emphasizes that the implications of the name "amebic dysentery" has tended to exclude consideration of amebiasis in a large number of cases, and further that the surgeon must therefore commonly diagnose a complication, amebic hepatic abscess, in the absence of any signs of the primary disease. Whether or not diarrhea is present, the stool usually contains cysts, trophozoites, or both. In 55 cases of this series stool examinations were done with positive findings in 40. Because of the great value of a positive stool examination in the diagnosis of amebic hepatic abscess, stool examination should be done upon the slightest suspicion of the presence of this lesion. Saline catharsis is helpful in raising the incidence of positive stools.

Certain standard etiological relationships are usually considered in developing the diagnosis. In this series there were only 5 women. No patient was under 20 years of age, and the age distribution is relatively even after the thirtieth year. Although alcoholism has been thought to predispose to the development of amebic hepatic abscess, such could not be concluded from our cases. However, a seemingly important relationship does exist between trauma and amebic abscess. In 3 instances the patient was entirely well at the time of a very considerable trauma to the liver region, and immediately developed symptoms subsequently proved to be due to amebic abscess. This has considerable medicolegal significance and also necessitates the inclusion of amebic abscess in the differential diagnosis of the sequelae of liver trauma. Further, this suggests that amebic infestation of the liver is compatible with an absence of any significant lesion, because trauma could only operate by determining the activation of a latent infection.

Turning from the foregoing general implications, the diagnostic problem must be clarified by consideration of the various syndromes presented by patients with amebic hepatic abscess. Incorrect diagnosis accounted for more deaths than occurred in the treated patients in this series, from a hospital quite alert to the presence of the disease. Ten cases were not recognized before necropsy, and an approximately equal number probably existed in deaths in which necropsy was not done. This total would exceed the 16 deaths in our 63 treated patients. This diagnostic difficulty is due to the fact that, at least in Southern California, amebic hepatic abscess presents many manifestations not included in its description in textbooks or in the literature from the Orient. Instead of regularly being chronic, in 58 per cent of our cases the process was an acute severe disease. A second important general feature is that instead of the lesion being one which almost exclusively presents in the right upper quadrant, in 33 per cent of our cases abdominal features were absent or minimal and the clinical phenomena were pulmonary, because the abscess was located in the dome of the liver.

From the Department of Surgery, University of Southern California.

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Because of these two fundamental variations, four syndromes are seen: an acute costal margin syndrome, a chronic costal margin syndrome, an acute pulmonary and a chronic pulmonary syndrome. Each of the four involves a separate field of differential diagnosis. The chronic syndrome at the costal margin includes the classical cases. These may be misdiagnosed as malignancy of the liver, stomach, gall bladder, or colon; cirrhosis, amyloid disease, echinococcus cyst, pancreatic cyst, or hepar lobatum. The acute syndrome at the costal margin is more frequently misdiagnosed, and is usually mistaken for acute cholecystitis or penetrating, or perforated duodenal ulcer, or abscess complicating either peptic ulcer or cholecystitis. The chronic pulmonary syndrome closely resembles cancer of the lower lobe when chronic pneumonitis exists without pleural effusion, whereas if effusion exists tuberculosis or cancer are usually considered responsible. In the acute pulmonary from "basal pneumonia" is repeatedly diagnosed and empyema is added when effusion occurs, or an acute pleurisy with effusion is considered to be present. In such cases a bronchial fistula may fortunately occur, and the appearance of anchovy sauce sputum develops a correct diagnosis. If the left lobe of the liver be involved by amebic abscess, again the process may be acute or chronic, and the phenomena occur in the epigastrium rather than at the left costal margin, and if transphrenic effects appear, they are likely to be pericardial. In order to attain any high degree of clinical accuracy, amebic hepatic abscess must consistently be added to the possibilities in differential diagnosis in each of the foregoing situations.

A few general diagnostic considerations should be emphasized. Hepatomegaly is a constant feature, often detectable in the bedside examination, and usually demonstrable by roentgenological study. Even with dome abscesses there is often downward enlargement. In the very chronic cases an abscess may point and produce a mass which can be recognized to be arising from the liver. One of our patients had such a mass for 20 years and the condition simulated very closely echinococcus cyst of the liver.

When the phenomena of amebic abscess are superior instead of anterior, x-ray study will accurately reveal the phrenic or transphrenic effects. The most characteristic changes are, as emphasized by Ochsner, anterior and medial in the lower right chest. Elevation and immobility of the diaphragm are the earliest findings. Pneumonitis or pleuritis alone or in combination occur as the lesion progresses.

The systemic features are not specific and parallel the extent and acuteness of the liver lesion. Two aspects should be emphasized. First, night sweats are frequent in the chronic cases and should serve to raise doubt if the case has been diagnosed as cirrhosis or carcinoma of the liver. Second, in the acute cases, chills may be so outstanding as to suggest the presence of pylephlebitis or malaria, or if jaundice exists, a cholangitic basis is suspected.

TREATMENT

The primary basis for cure of amebic abscess is emetine in sufficient dosage. Amebic abscess is a special type of liver necrosis, as is a gumma, and emetine is approximately as much a specific as neoarsphenamine. If amebic abscess were looked upon as being similar to a broken down gumma, with aseptic evacuation of its contents often required to eliminate a foreign body factor, the proper orientation for treatment would be established. Two factors have tended to confuse the situation: first, the frequent gross resemblance to, or the possible actual presence of, bacterial infection, and, second, timidity in administering adequate amounts of emetine.

The resemblance to bacterial infection may be striking. In a third of this series the abscess content was not anchovy sauce pus but rather was creamy white puriform material. In a number of instances it had a very foul odor. Aerobic and anaerobic cultures of this foul material remained sterile. Except in 3 cases in which extensive lung and diaphragm destruction existed, every abscess in our series was sterile, although the incidence of secondarily infected abscesses is given in the literature as 14 per cent.

Hesitation in giving adequate emetine is dependent upon fear of its capacity to injure the myocardium. As a result many patients with amebic abscess of the liver have retained possession of excellent hearts but have died of insufficiently treated amebic abscess. We do not advocate indifference toward the dangers of emetine, but since amebic abscess is a fatal disease, the amebas must be destroyed. Our patients have usually been given 1 grain daily, intravenously or intramuscularly, for 6 doses, then a rest for 6 days and the course repeated as necessary. As much as 24 grains have been given in this way and not one cardiac problem has developed. Under extreme conditions the rest period should be lengthened. Electrocardiography in conjunction with close observation of the blood pressure and reactions of the patient are of great help in controlling the therapy. Intramuscular administra-

tion exposes the heart to lower concentrations of the drug than does intravenous administration.

RESULTS OF TREATMENT

In our series there are 3 groups of cases, those apparently cured with emetine only; those requiring aspiration in addition to emetine; and those who were treated surgically with or without emetine.

Cases treated with emetine only. When the diagnosis of amebic abscess has been made our patients have been routinely given emetine as described. Frequently a very favorable response occurs, and with continuation of the drug, apparent cure takes place. Nineteen patients were treated in this way with complete recovery in all. The largest total dose of emetine was 16 grains, the average 9.5 grains. The drug was administered intravenously in 10 and intramuscularly in 9. In this group are 4 cases with negative aspirations. We assume that the aspirations were technical failures, but they may represent the supposedly beneficial effects of hepatic phlebotomy. Also there are 3 cases of bronchohepatic fistula. The majority of this entire group were initially clinically indistinguishable from the group requiring aspiration; however, they could have been amebic hepatitis, or cases with a small abscess, or represent infection with very emetine-susceptible strains.

There are other chemotherapeutic aspects to the problem of hepatic amebiasis. In one of the other groups a patient being given emetine deteriorated steadily after liver drainage but improved rapidly when yatren therapy was instituted although there were no colon symptoms. This may be significant in the treatment of "emetine resistant" cases of amebic hepatic abscess. The colon problem is important in two ways: First, the mortality in the group with active colon disease is considerably higher than in the cases with latent colon infection. This indicates the need for active colon therapy in the group with active colon lesions. Second, in all cases the colon infection must later be treated as a part of the program to prevent reactivation of the liver process. This hazard is exemplified in our series by 5 cases in which patients had previously had amebic abscess 1 month, 2 years, 5 years, 9 years, and 13 years, respectively. Part of these may have represented new liver infections while the remainder indicated reactivation of old abscesses. An aid in measuring inactivation of the infection is the blood sedimentation rate, and, used in a small group of this series, it has constituted an important guide in indicating the need of further treatment, when on clinical grounds it would have been discontinued. In the 24 cases in which autopsy was carried out the number of abscesses found varied from 1 to 8; all were on the right except in 2 cases with 1 each on the left in addition to the 2 on the right in 1 case and 1 on the right in the other. The diaphragm was perforated in 6 and not perforated in 18. There was a colon lesion in 14 and none in 10; a colon perforation was noted in 4 cases and in 1 of these there was noted also a perforated amebic appendicitis.

Cases treated with emetine and aspiration. A second group of cases are those in which, after emetine has been started, the response is not satisfactory, or a mass exists, or a very large liver. In these aspiration becomes necessary, and it may require repetition. For this procedure a cerebral ventricle needle is an excellent instrument; it is of large bore, carries a stylet, and is quite blunt, favoring minimal danger of hemorrhage. The skin and underlying fascia may be nicked with a shart pointed scalpel to facilitate its passage. If an area of edema or localized tenderness exists, aspiration should be done at that point. If a mass exists, aspiration should be done directly into it. The problem cases are those in which localizing physical signs do not exist, and these are usually dome abscesses. It is usually recommended for such cases that aspiration be done through the tenth intercostal space in the anterior axillary line and that if the needle be passed upward, inward, and backward not more than 3.5 to 4 inches, the great vessels will not be injured. We believe that dome abscesses are readily missed by this technique and prefer to aspirate high along the right costal margin, going upward, outward, and backward. In no case has emetine or lipiodol been injected into the abscess cavity. Routine smears should be made at once to exclude the presence of bacterial infection. In the series herein reported treated by emetine and aspiration there are 18 cases and no deaths. The amount of emetine given varied from 4 to 24 grains; the injection being intravenous in 15 and intramuscular in 3. Three required 3 aspirations and the largest amount aspirated at any one time was 2200 cubic centimeters, the lowest 45 cubic centimeters. Two cases are included in which at the time of laparotomy an abscess was discovered, the abscess was aspirated, and the abdomen was closed without drainage. The question of multiple abscesses requires consideration. In 7 of the 24 autopsies, multiple abscesses were present. In none of the treated cases was more than one recognized. This discrepancy could be explained

by supposing that, during aspiration of an abscess, the lowered pressure would tend to break down the wall of an adjacent abscess, or that emetine controlled a small second abscess. We probably had no treated cases with widely separated large abscesses.

Cases treated surgically. The surgically treated group comprises 26 cases, 14 adequately treated with emetine. The mortality was 53 per cent. This group is in no way comparable to the previous group. In 4 there were acute intraperitoneal ruptures, and patients were operated upon for duodenal perforations and 3 survived. If such an abscess is small and has emptied itself drainage is of no value, while if it is large and still leaking, a short period of drainage is indicated. In 2 cases rib resection was done for secondary infection of the pleura. Of these 2, 1 lived and the other died with the empyema practically healed, and at autopsy an active small amebic liver abscess communicating with a bronchus was still present. Many amebas were present even though 16 grains of emetine had been given, probably an emetine resistant strain. Ten of the 12 remaining deaths were in the 10 cases given practically no emetine. One death was due to open drainage with a resultant postoperative bacterial infection of the liver. It may be stated that surgery usually is necessary in 4 situations: for safety in exposing left lobe abscesses, for acute rupture because the diagnosis cannot be made, for pyogenic complications in the pleural cavity, and for drainage of amebic abscess complicated by bacterial infection. For the usual case the stress of surgery, and the danger of secondary infection combined with the evidence that it is unnecessary, should make it reasonable to conclude that the indications for surgery should be confined to those described.

Of the 26 patients operated upon emetine in doses varying from ½ grain to 25 grains was given in 19 cases, not given in 7 cases. The intravenous route was used in 10, the intramuscular in 9.

CONCLUSIONS

Our conceptions of the foregoing problems have been restricted by the implications in the names "tropical abscess" and "amebic dysentery." The disease is in no way confined to the tropics; the liver lesion is not, in the usual sense, an abscess; and "amebic dysentery" actually describes only the severe form of amebic colitis. The resultant restricted conceptions have served as a basis for innumerable diagnostic failures. Realization that amebiasis is endemic in temperate climates; that "amebic hepatic abscess" is a special type of liver necrosis, for which there is specific chemotherapy; and that amebic colitis is commonly asymptomatic, will help in creating more frequent suspicion of the presence of the disease and improve the therapy applied.

METAPLASIA AND CARCINOMA IN CERVICAL POLYPS

JACOB MEZER, M.D., Brookline, Massachusetts

A CERVICAL polyp is simply a localized heaping up of normal cervical tissue. It may have a squamous or a columnar epithelial surface and its core may be fibrous tissue (fibrous polyp) or glandular as well (mucous polyp). Although its origin is obscure, inflammatory lesions of the cervix are most frequently the background.

Cervical polyps are usually red, pedunculated, and fragile, and may be the cause of intermenstrual or contact bleeding. According to Israel, 14 per cent of office patients presenting themselves because of irregular bleeding were found to have cervical polyps, whereas 2.4 per cent of consecutive gynecological patients admitted to the hospital for any cause were found to have polyps. Geiger states the incidence to be 1.5 per cent of 2,048 patients seen at the Cook County Hospital. The occurrence is placed as high as 10 per cent by Fetterman who studied 1,000 gynecological patients.

There is general agreement that cervical polyps appear most frequently in the fifth decade and in parous women (7). As many as 43 per cent are asymptomatic as far as the polyp itself is concerned. However, it has been noted by many that associated gynecological pathology is very often found.

SQUAMOUS METAPLASIA

In cervical polyps as well as the cervix, subject as they are to trauma, bleeding and inflammation, squamous metaplasia is a process often seen, sometimes atypical, and not infrequently diagnosed as "precancer" or even cancer, for which extensive therapy is given. Superimposed cancer may be missed when a disorderly, anaplastic and undifferentiated epithelium is ascribed to an inflammatory or metaplastic change. Because inflammation is so frequently associated with squamous metaplasia (or epidermization), cause and effect relationship has naturally been thought to explain the latter. Meyer (9) believes that during inflammation, the columnar epithelium is hyperactive, extends outward to the portio vaginalis where it becomes eroded only to reappear during the first stage of healing when it forms new glands. As the healing continues, the squamous epithelium again asserts itself as metaplasia, pushing the columnar epithelium back to the external os, in a reparative process.

These stages of healing are interchangeable. Meyer explains the finding of metaplasia high in the endocervix or in the endometrium on the basis of squamous epithelial "rests" left stranded as a result of interplay of the stages of healing, and cites evidence that in the 6th month of embryonic life the indifferent squamous epithelium lining the cervical canal is pushed out by the developing columnar epithelium. Novak believes that genuine metaplasia may take place from columnar to squamous epithelium, but not from squamous to columnar. Fluhmann concludes that metaplastic squamous epithelium is derived from infraepithelial indifferent cells which become converted into squamous epithelium as a result of inflammation and crowd out the columnar cells.

That squamous metaplasia is a process frequently encountered is attested to by Fluhmann, who found it in 29 per cent of 100 cervical polyps. Of 1,195 specimens of cervix examined, 59, or 4.9 per cent, were found to have metaplasia. He felt that since metaplasia (or "epidermidalization") is so frequent in polyps and cancer so rare, metaplasia would seldom if ever be the forerunner of cancer. However, certain atypical forms were so disturbing as to make differentiation from cancer quite difficult. In these borderline cases, three principles are of help in making the decision (Schauenstein, Pronai, Rubin, Ewing, Fluhmann, 5):

1. *Atypical properties of individual cells*—dark and dense staining characteristics, irregular nuclei, absence of regular order, atypical and asymmetrical mitoses are properties of malignant neoplasm.

2. *Differentiation of tissue*—In malignant neoplasms, the basal epithelium is irregular in arrangement and the cells lie obliquely or transversely to the surface. In epidermidalization, the cells lie in normal or parallel lines.

3. *Invasive and destructive properties of the proliferating cells.* (Although pearls are found in malignant neoplasms, they are not pathognomonic of malignant growth since they are found in normal tissue.)

From the Free Hospital for Women, Brookline, Massachusetts and the Department of Gynecology, Harvard Medical School, Boston.

Presented at the Clinical Congress of the American College of Surgeons, November 6, 1941.

CANCER

How often does carcinoma arise in cervical polyps? Martzloff has had the same experience as Cullen in not finding a single bona fide instance of a malignant cervical polyp after an extensive study of cancer of the uterus, but presents a very convincing photomicrograph of an early squamous carcinoma *in situ* which he calls "superficial cancer." That this is, indeed, cancer and progresses to invasion and destruction if untreated, has been demonstrated clinically at the Free Hospital for Women (12, 13, 16), where all such lesions (usually found in routine biopsies of Schiller positive areas in the out patient department) are regarded as cancer and treated as such. Meyer has repeatedly called attention to this early malignant lesion (10). Perhaps the failure to recognize this early cancer has led to the popular misconception that any cervical polyp is undoubtedly benign and therefore does not warrant the trouble and expense of pathological examination. As opposed to this point of view, is that of Witherspoon who states that 5 per cent of polyps are malignant, and Fetterman who places the incidence as high as 6 per cent in 100 cervical polyps studied. It may be that this high incidence is due to the inclusion of cases of atypical squamous metaplasia as cases of malignant neoplasms. Other estimates as to the incidence of malignant growths in polyps are between those two extremes. Israel has found 1.7 per cent of 117 polyps to be cancerous; Geiger, 3.1 per cent of 32; Day, 0.33 per cent of 300; Fluhmann, 2 per cent of 100; and Condit, 0.5 per cent of 200. Other isolated cases of carcinomatous polyps are reported (2, 14).

CASES AT THE FREE HOSPITAL FOR WOMEN

The recent finding within 5 days of 2 patients having cancer superimposed on an otherwise benign cervical polyp stimulated a study of the microscopic slides in all cases of cervical polyps removed at the Free Hospital for Women. From September, 1902, to October, 1941, there were slides available in 1,636 cervical polyps. Of these, 513, or 31.4 per cent, were found to have squamous metaplasia, or epidermization of glands. This metaplastic process varied from mild to marked degree. Of these 1,636 cases, 5, or 0.37 per cent, were found to be complicated by carcinomatous changes. Two were adenocarcinomas, and 3 were squamous carcinomas. Two of these had originally been judged benign; one patient is untraceable, and the other is still alive after 12 years. Four of the polyps showing marked atypical metaplasia had originally been judged malignant, and all were treated as such, the patients now being alive and well—5, 2½, 2, and 4 years later, respectively. It is notable that all 5 carcinomatous polyps are associated with squamous metaplasia, and that in 3, the metaplastic epithelium is cancerous. This would tend to show that metaplastic epithelium, though undoubtedly benign (1 out of 3 polyps, roughly, showed this change), is not immune to malignant change. The fact that 1 polyp in 325 (5 in 1,636) was malignant would show that the epithelium over cervical polyps, just as over the cervix itself, may be the seat of malignant growth. No instance of undoubted sarcoma definitely arising in a cervical polyp was found.

Squamous Metaplasia in Cervical Polyps

CASE 1. Mrs. H., No. S-39-2022, (Fig. 1), a 49 year old octipara, on September 2, 1939, had a cervical polypectomy incident to the treatment of prolapse. The polyp had led to no symptomatology. *Microscopically* was seen a cervical polyp with a chronically inflamed connective tissue core. The surface squamous epithelium showed keratohyalin deposition (leucoplacia) in the superficial layers with hyperkeratosis. Near the base of the polyp, the squamous epithelium became metaplastic and grew down under the framework of the columnar glandular epithelium where it appeared in patchy distribution. The framework was intact and was the skeleton for the metaplastic epithelium which grew down regularly along the lines laid down for it by the columnar epithelium.

CASE 2. Mrs. R., No. S-41-248, (Fig. 2), a 49 year old quadripara, complained of dysfunctional flowing for 2 years and prolapse. An incidental polyp was removed on February 6, 1941, and the cervix was cauterized. An early adenocarcinoma of the endometrium found on curettage required subsequent hysterectomy. The patient was alive and well 8 months later. *Microscopically* the polyp was the seat of marked chronic inflammation with plasma cells present in abundance. The metaplastic process was more developed here, the entire surface being covered by metaplastic and columnar epithelium. Numerous fragile projections were seen on the surface. Incident to the marked inflammation, the cervical glands had become markedly tortuous and ended in adenomatous configurations. Thus the skeleton was laid down for a very intricate arrangement of metaplastic epithelial proliferation. In one area the erosion was not yet covered by epithelium.

CASE 3. Mrs. Mac P., No. 27796, (Fig. 3), a 47 year old primipara, had a polypectomy, cauterization of the cervix and supravaginal hysterectomy for multiple fibroids, on April 12, 1937. She had complained of low abdominal pain, recent menorrhagia, and incontinence. She did not return for follow up. *Microscopically* the cervical polyp showed the original glandular arrangement mostly replaced by metaplastic epithelium which, however, still maintained its benign nature. The irregular processes of squamous epithelium intricately arranged were so angry looking because of the adenomatous nature of the original mucous glands which were being undergrown and replaced, but not invaded.

CASE 4. Mrs. S., No. 25682, (Fig. 4), a 44 year old sextipara, had complained of menorrhagia for 3 months, but there had been no intermenstrual bleeding. A small cervical polyp was excised and the cervix was cauterized on February 11, 1936. Because the original diagnosis was

Fig. 1. Case 1. Cervical polyp with beginning metaplasia. ×95.

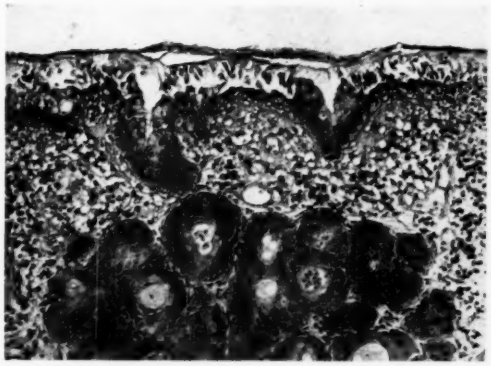

Fig. 2. Case 2. Cervical polyp with squamous metaplasia and "adenoma." ×95.

Fig. 3. Case 3. Cervical polyp with marked squamous metaplasia. ×95.

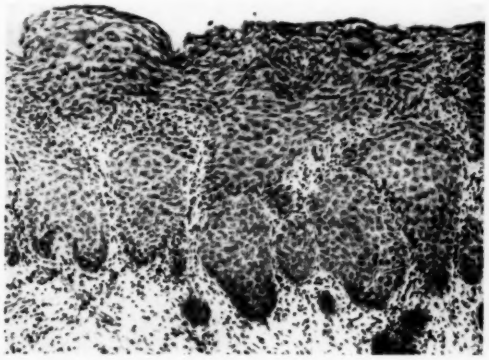

Fig. 4. Case 4. Cervical polyp with marked atypical metaplasia. ×95.

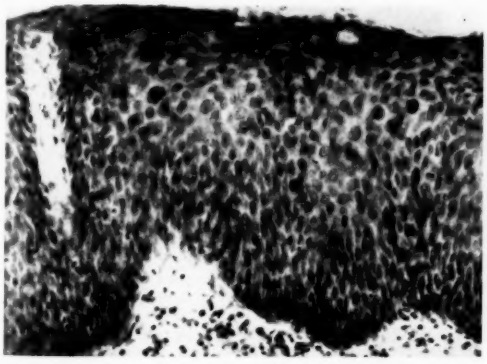

Fig. 5. Case A. Squamous carcinoma in cervical polyp. ×185.

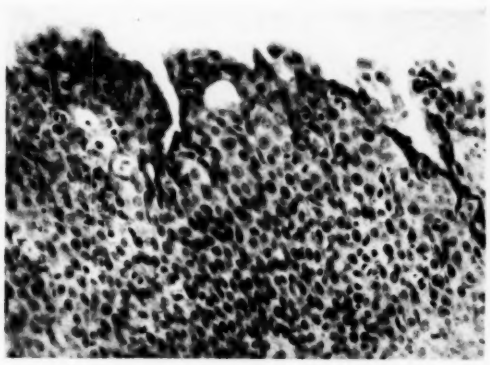

Fig. 6. Case B. Cervical polyp with squamous carcinoma starting in metaplasia. ×185.

that of a grade I squamous carcinoma, a total of 5400 milligram hours of radium and 4800 roentgens of x-ray was given. The patient was alive and well 5 years later. *Microscopically* there was seen a cervical polyp in which no glands were left. The squamous metaplastic epithelium had grown exuberantly and even pearls were beginning to make their appearance. Occasional symmetrical mitoses were seen in the basal layers. However, there was good organization and no anaplasia of the cells. This intricate picture was the end-result of marked chronic inflammation with adenomatous formation of cervical glands, undergrowth, and final replacement of glandular epithelium with metaplastic epithelium. This polyp was benign.

Carcinoma in Cervical Polyps

CASE A. Mrs. Sch., No. 16867, (Fig. 5), a 47 year old primipara, was seen in the out patient department on July 8, 1929, because of frequent and prolonged periods for 1 year. A 1 centimeter cervical polyp was excised and reported benign. The patient was still alive after 12 years. *Microscopically* the polyp was covered by columnar epithelium but here and there by metaplastic but malignant squamous epithelium which was growing down in processes, invading and destroying the somewhat dilated glands. The cells were dark staining, disorganized, and showed numerous mitoses even in the surface epithelium.

CASE B. Miss B., No. 19495, (Fig. 6), a 54 year old, unmarried nullipara, with menopause 1 year before, complained of prolapse. On September 29, 1931, an incidental asymptomatic 1½ centimeter polyp was removed and the base was cauterized. The endometrium was atrophied. The polyp was reported as benign. Seven months later the patient was living and well. She is now untraceable. *Microscopically* the polyp showed moderate evidence of metaplasia. However, in one surface area, the metaplastic epithelium was thickened by an exuberant middle layer growth of cells which were undifferentiated, dark staining, and presented innumerable mitotic figures per high power field. There was as yet no invasion.

CASE C. Mrs. M., No. 22268, (Fig. 7 and 7a), a 38 year old secundipara, entered the hospital because of periods which came every 2 weeks for 9 months and daily bleeding which had occurred for 3 months. On November 8, 1933, a friable cervical polyp in the midst of crumbly cervical tissue was removed. A total of 5400 milligram hours of radium and 4800 roentgens of x-ray was given. The patient was alive and well 7¼ years later. *Microscopically* the polyp was covered by a malignant squamous epithelium composed of dark staining undifferentiated cells invading the stroma and the neighboring glands. There was variation in size and shape of the nuclei and numerous mitoses were seen. The surrounding cervical tissue was also invaded.

CASE D. Miss St. J., No. S-41-2074, (Fig. 8 and 8a), a 49 year old unmarried nullipara entered because of low abdominal pain for 15 years, irregular periods, and hot flashes for 4 years, and discharge. On September 9, 1941, a 1 centimeter cervical polyp was removed and a 3 centimeter pedunculated submucous fibroid was also removed. *Microscopically* the surface of the polyp was eroded and the stroma was edematous, infiltrated with acute and chronic inflammatory cells. The endocervical glands had lost their mucous secretory activity and were arranged in close association with benign squamous metaplastic epithelium. These glands were intricately arranged in groups and extremely piled up, growing in papillary processes into the lumina. The intricate reduplication, hyperchromatic nuclei, and frequent mitoses gave evidence of malignancy.

On December 9, 1941, complete hysterectomy with bilateral salpingo-oöphorectomy was performed. No malignancy was demonstrable in the excised specimen.

CASE E. Mrs. A., No. S-41-2107, (Fig. 9 and 9a), a 49 year old primipara, entered the hospital because of frequent prolonged periods for 4 months, with bright red bleeding for 2 days after each period. A Manchester-Fothergill operation was done, on September 13, 1941, for prolapse and a 2 centimeter polyp was removed, together with the cervix. *Microscopically* the polyp showed squamous metaplasia. However, in two of the tortuous endocervical glands, the lining cells were actively growing and had lost their mucous secreting activity. Papillary projections were growing into the lumina and down into the surrounding tissue. The nuclei varied in size and shape, were hyperchromatic, and showed frequent mitoses, some of which were bizarre.

Because the polyp had been attached to the removed cervix, this patient was to be watched closely without further therapy at this time.

ANALYSIS OF CASES

Although these 5 cases of carcinoma in cervical polyps vary in age from 38 to 54 years, the average age of 47 years is well in the fifth decade. Two occurred in unmarried nulliparous women, and only 1 in a patient beyond the menopause. One polyp was entirely incidental, whereas the 4 others were in patients who complained of irregular periods. Intermenstrual bleeding attributable to the polyps was seen in but 1 patient, who had a fully developed malignant growth. Thus, if we are to make an early diagnosis of cervical cancer, routine speculum examination of every female patient should be done, as well as bimanual examination. A nonbleeding polyp should be excised at the base, and the base should be cauterized.

In cases of abnormal bleeding, one should not be lulled into a false sense of security by finding and removing a cervical polyp. Simple excision of such a polyp may delay the diagnosis of some other coexisting cause of bleeding. Such a patient should have a careful pelvic examination. The cervix should be meticulously examined for suspicious areas often identified by failure to stain with Schiller's solution. If advisable, therapy should be delayed until the nature of these lesions can be shown microscopically. Careful curettage of the endocervix and the endometrial cavity should be done to rule out these areas as foci of malignancy.

Polyps should not be thrown into the waste basket, but should be studied by the pathologist in every case. If squamous metaplasia is found, there need not be any fear of cancer or precancer.

The incidence of malignancy of 1 in 325 may be low, since once cancer of the cervix is advanced, it is impossible to tell whether the cancer started in a polyp or not.

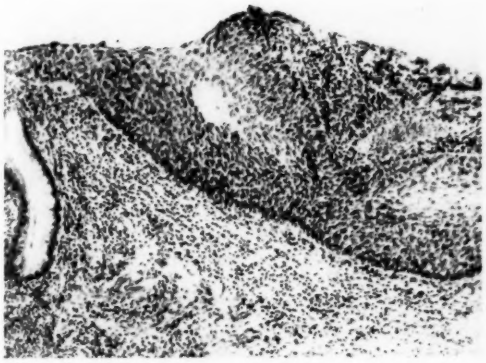

Fig. 7. Case C. Cervical polyp with squamous carcinoma. ×95.

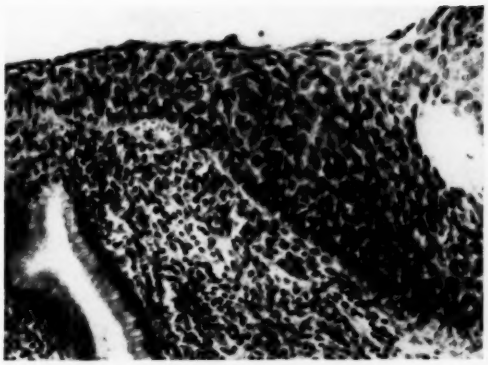

Fig. 7a. Case C. Cervical polyp with squamous carcinoma. ×185.

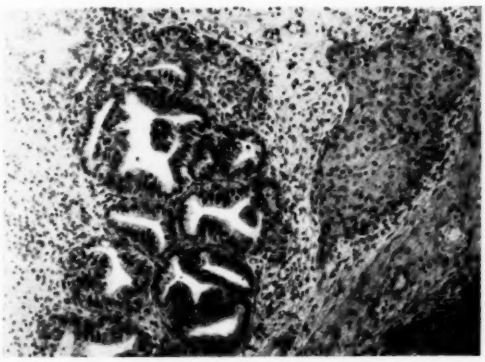

Fig. 8. Case D. Cervical polyp with adenocarcinoma. ×95.

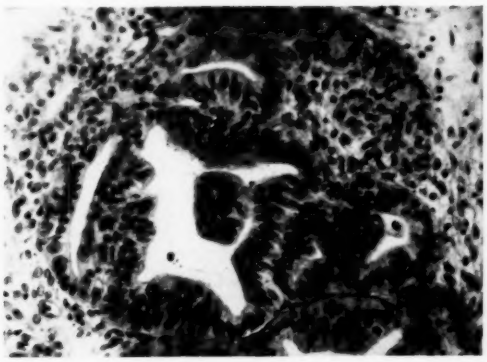

Fig. 8a. Case D. Cervical polyp with adenocarcinoma. ×185.

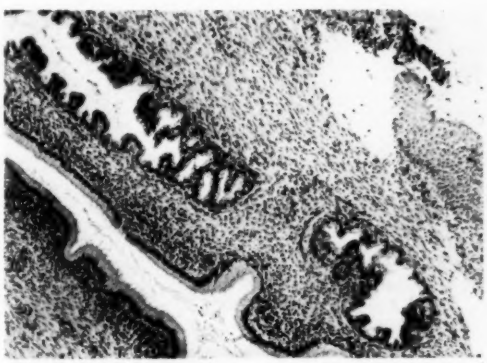

Fig. 9. Case E. Cervical polyp with adenocarcinoma. ×95.

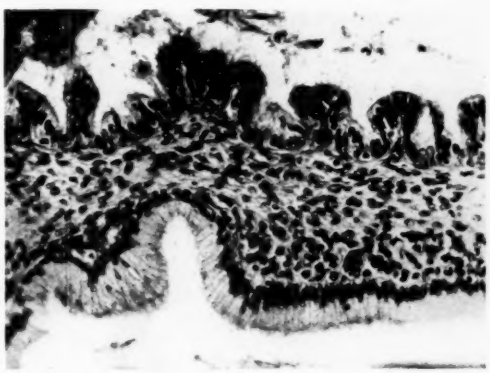

Fig. 9a. Case E. Cervical polyp with adenocarcinoma. ×185.

SUMMARY

1. Cervical polyps are frequently found in gynecological patients.

2. A third of the polyps studied were subject to squamous metaplasia, or "epidermization," which is neither a precancerous nor a malignant process.

3. Criteria are cited for the diagnosis between metaplasia and cancer.

4. The development of squamous metaplasia is exemplified.

5. Five cases of carcinoma which arose in cervical polyps are cited among 1,636 polyps studied.

6. Cervical polyps should be removed and their bases cauterized.

7. In cases of abnormal bleeding, other causes should be ruled out by means of careful pelvic examination before the cervical polyp is accepted as the only cause of this bleeding.

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GRANULOSA CELL TUMORS OF THE OVARY

WILLIAM H. HARRIS, Jr., M.D., New Orleans, Louisiana

THE subject of granulosa cell tumors of the ovary has received a great deal of attention in the literature, especially in the last 10 years. Many very comprehensive reviews of the subject with case reports have appeared. The purpose of this paper is to discern certain features relative to incidence, endocrine influence, histogenesis, and pathology, and to emphasize especially the question of possible malignancy of these tumors. It has been our good fortune to encounter at autopsy a case of granulosa cell carcinoma of the ovary, in which there was metastasis to the gastrointestinal tract. In the American literature, the actual descriptions of metastatic lesions are few. Bell and Datnow present a photomicrograph of a section of metastasis in the omentum from Dodd's case of a granulosa cell carcinoma. The German literature contains several reports of metastatic lesions. Another feature, which is somewhat different in our case, is that death resulted from cardiorenal failure and the granulosa cell tumor was an incidental finding at autopsy. Bland and Goldstein (2), in a review of 311 cases, note that in only 2 was the granulosa cell tumor found at necropsy.

HISTORY

The history of granulosa cell tumors has been covered very thoroughly in other publications. Robinson states that early descriptions were given by Rokitansky in 1885 and Acconci in 1888. Usually, as stated by Pratt, von Kahlden is credited with the earliest definite description of the entity. He reported a case of "adenoma of the graafian follicle, with transition to malignancy" in 1895. The name, "granulosa-cell tumor of the ovary," was first used by von Werdt in 1914. R. Meyer followed with publications in 1915. He has subsequently done much towards clarifying the subject.

OCCURRENCE

In 1939, Dockerty and MacCarty noted that there had been approximately 300 cases of granulosa cell tumors reported. In the American literature, however, until 1930, there had been only 3 cases reported (30). Bland and Goldstein (2) collected 311 cases, which they used as a basis for their paper. Other series often referred to are those of Novak and Brawner (18); Te Linde; Daily; Meyer; Schulze; Klaften; Szathmary (quoted from Thornton); Habbe; Lepper, Baker and Vaux; and Wolfe and Kaminester (34). As will be noted, many of these are German authors. It is, therefore, obvious that while the German literature contains numerous case reports, the number of cases in the American literature is relatively few. It is no longer believed that granulosa cell tumors are a rarity, but they are infrequent enough and the details of the pathology concerned are sufficiently clouded to warrant other reports and closer attention.

From the Department of Pathology, Tulane University School of Medicine and the Charity Hospital.

PATHOLOGICAL PHYSIOLOGY

One of the features of granulosa cell tumors that has aroused most interest is their endocrine aspect. The endocrine significance of these tumors has been discussed, according to Butterworth, by Schroeder, Neumann, and R. Meyer. Meyer states that cells of a new-growth may exhibit a specific functional capacity corresponding exactly to the function of the tissue from which they arise. Thus ovarian neoplasms may functionate and participate in the process of development of secondary sex characters. The hormone produced is "folliculin" or the estrogenic hormone. In a case of granulosa cell tumor in a woman 9 years past the menopause, Schuschania made quantitative estimations of folliculin. During a 5 day period before operation for removal of the tumor, there were 326 mouse units of folliculin in the urine and 619 mouse units in the feces. In the 8 days following operation, there were only 158 mouse units of folliculin in the urine. Sixty-six days after operation, no folliculin was demonstrable in urine or feces. Palmer also made determinations of the excretion of estrogenic hormone by a patient with granulosa cell tumor. He found that the amount of the hormone excreted daily by this patient was about four to five times the average daily excretion by normal nonpregnant women, and about equal to the amount excreted daily by a woman 6 to 8 weeks pregnant. However, a normal woman may excrete more estrogenic hormone in a single 24 hour period during the peak of hormone excretion (the midintermenstrum) than was excreted daily by this patient with the granulosa cell tumor. But this

patient was bleeding while excreting the hormone, and, normally, estrogen excretion is lowest at the menses. Palmer also found that the tumor in his case contained 11.7 milligrams of estrogenic hormone per kilogram of desiccated tumor. After operation, hormone excretion became normal. He further suggests that some of the hormone may be lost in the vaginal bleeding, and, therefore, the excretion of hormone by the kidney will be diminished in these cases. Bland and Goldstein (2, 3) report a very interesting case of a 7 year old girl. This child showed precocious puberty. She was operated upon and a granulosa cell tumor of the left ovary was removed. Eighteen months later, she returned to the hospital and a second laparotomy disclosed a granulosa cell tumor of the right ovary, which was removed. Before each operation, there were large quantities of estrogenic hormone in the blood and urine, which disappeared after operation. Six months after the second operation, the estrin pregnancy test of blood and urine was negative. Frank has done considerable work on the biological significance of ovarian growths in children. The test used by him for determining the estrogenic hormone content of blood requires 40 cubic centimeters of blood. This, as he states, is too large an amount for children. Therefore, in children, female sex hormone tests should be done on urine.

Even very tiny tumors are capable of evoking profound body changes, as noted by Novak (17). With their production of folliculin, the features usually noted are those of effects of excess of this hormone; i.e. precocious puberty, return of vaginal bleeding after menopause, menstrual disturbances in active sex life, hyperplastic proliferative endometrium, possible breast changes. Bleeding may be quite regular (17), suggesting that "insofar as mere periodic bleeding of the menstrual cycle is concerned, folliculin plays the all-important rôle," being possibly an automatic and self-regulating mechanism with pituitary interrelation.

Countiss, Powell and Black, and others have reported cases of granulosa cell tumors in which, within 6 months to a year after removal of the tumors, pregnancy developed. This supports the belief that there is a rapid return to normal of the hormonal and reproductive system, following removal of these tumors. As Countiss states also, it suggests that large doses of estrin over long periods of time should produce no permanent ill effects on the reproductive system.

Besides the aspects of estrogenic hormone production in these cases, there are apparently other biological effects. The Aschheim-Zondek test has been positive in a number of instances. Bland and Goldstein (2) suggest that this is evidence of compensatory effort of the anterior pituitary gland to counterbalance the ovarian activity. Some of these tumors may also produce progestin. These features have not been adequately studied and need more attention.

Thus, the endocrine aspect of granulosa cell tumors is of importance from the standpoint of the tumors themselves, and also because an opportunity is afforded for further study of the effects of certain hormones and the interrelationship of the endocrine system as a whole.

PATHOLOGY

Incidence. In the series of Szathmary, there were 0.9 per cent granulosa cell tumors in 1,114 ovarian tumors. In Klaften's series, the incidence was 4.04 per cent, and in Fauvet's, 1.4 per cent. Thus, taking these together there were 2.11 per cent granulosa cell tumors in a group of 1,728 ovarian tumors. Schulze found 4 cases among 43 ovarian carcinomas occurring in 7,500 gynecological cases over a period of 19 years. Thornton states that granulosa cell tumors constitute from 8 to 10 per cent of all ovarian carcinomas. The age incidence has been given by Dockerty and MacCarty as: 60 per cent occurring after the menopause, 30 per cent between puberty and the climacterium, and 5 to 10 per cent before adolescence. Te Linde states that the average age is 52 years, and that 75 per cent occur after the age of 45 years. According to R. Meyer, they are most frequent in women from 60 to 74 years of age. Fahmy, in an analysis of 937 cases of post menopausal hemorrhage, found 32 cases of malignant ovarian neoplasms among which there were only 3 granulosa cell tumors.

HISTOGENESIS

There are two main theories as to the origin of these tumors.

1. The first theory is that of R. Meyer, that granulosa cell tumors arise from embryonic cell rests located in the medulla of the ovary. Meyer states that granulosa cell tumors arise from unused embryonal granulosa cells in the medulla of the ovary. Masses of these cells are found in the ovary of every full term fetus. Such masses of cells have also been found in the ovaries of adults. These unused cells may remain in their undifferentiated state, which is characteristic for the embryonic ovary. Seemingly they can persist without further differentiation late into life. Thus, one is led to the assumption that, under certain, still unknown conditions they might at any stage

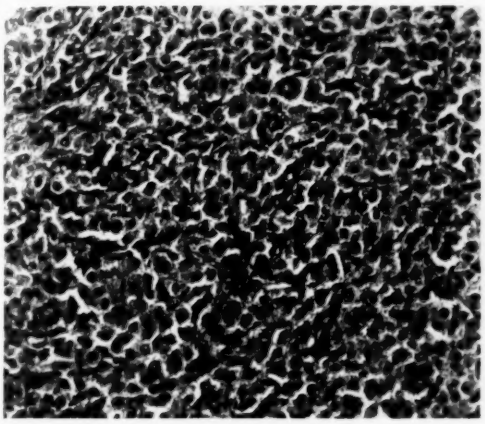

Fig. 1. Photomicrograph of section of a primary tumor in ovary showing diffuse arrangement of granulosa cells. ×135.

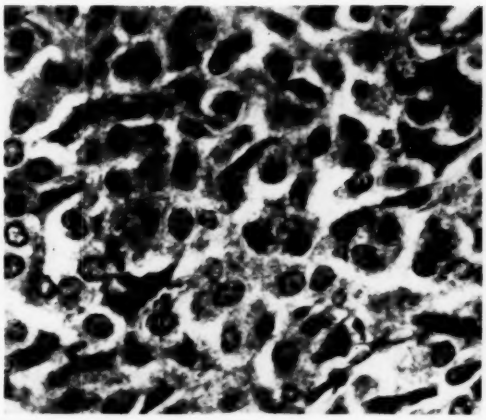

Fig. 2. Photomicrograph of primary tumor in ovary showing marked anaplasia of cells and hyperchromatic structure of nuclei. ×270.

in children or in elderly women be able to produce granulosa cell tumors. Meyer records having found proliferations of granulosa cells in the medulla of the ovary of a 40 year old woman. Te Linde also had a case in which there was an extremely early but completely formed granulosal cell tumor, situated in the medulla, near the hilum. In adult life, the follicles are limited to the ovarian cortex. Therefore, the origin of this very early granulosal tumor in the medulla practically excludes an adult follicle as its origin. In the medulla, there is much ovarian parenchyme which degenerates more or less completely before birth. By virtue of the position of this small tumor, then, it would seem that embryonal rests of this epithelium, very closely related to adult granulosal epithelium would be practically the only possible origin of this granulosal tumor in the ovarian medulla.

Schiller considers that granulosa cell tumors develop from relics of the normal mesenchymal core of the ovary. This infers, he says, that in the embryogenesis of the ovary, parenchymal remnants which did not enter into any relation with the ovulum, were left there. Years later, due to an unspecific stimulus, the inherent tendency of these cells to form female germ cords shows itself. Then there is first a cellular parenchymal proliferation, forming trabeculae. Eventually, ripe trabecular forms are noted. Finally, there appear follicle vacuoles, filled with liquid, but no ova (Call-Exner bodies). Schiller also points out the fact that granulosa cell tumors occur frequently in old women; this is evidence against the conception of the development of granulosa cell tumors from the granulosa of mature follicles—elderly women after the climacterium do not have any follicles and consequently no granulosa.

According to Novak and Brawner (18), granulosa cells are formed *in loco* from the ovarian mesenchyme from which likewise is formed the thecal and stromal tissue of the ovary. As they point out, this offers an adequate explanation of the apparent intermutability of the ovarian epithelium and connective tissue and of the frequent transitions between the two in granulosa cell tumors. Thus, the finding of sarcoma-like areas in a granulosa cell tumor is easy to understand. Furthermore, since granulosal and stromal elements are both derived from the same parent tissue, they may have the same physiological capacity to produce the female sex hormone. Thus, even an apparent sarcoma can exert biological influences no less potent than an epithelial tumor of the same histogenesis.

This theory of origin from embryonal cell rests is also supported by Wolfe and Kaminester (34) and Schulze.

The case report by Voight is of interest from the standpoint of histogenesis. In this case, there was a large granulosa cell tumor of retroperitoneal origin with development into the mesosigmoideum. He states that this case supports Fischel's mesenchymal theory of granulosa cell origin. The cases of Ragins and Frankel and of Powell and Black of intraligamentous granulosa cell tumors are somewhat similar. Compton reports a case of granulosa cell tumor of the left ovary, with the

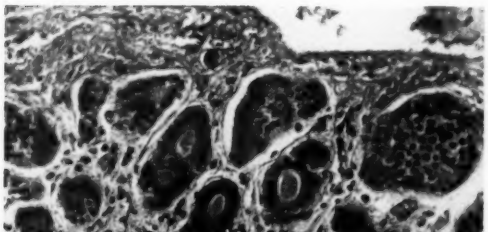

Fig. 3. Photomicrograph of section of a metastatic nodule on serosa of ileum illustrating typical follicle formations. ×135.

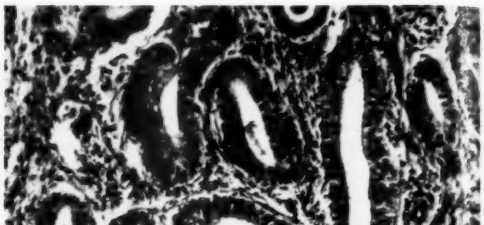

Fig. 4. Photomicrograph of endometrium showing this structure in persistent proliferative phase with marked thickening. ×135.

occurrence 16 years later, in the same patient, of another granulosa cell tumor in the right vesicouterine fold, which was not connected with the right ovary.

As quoted from Powell and Black, Fischel states that germ cells originate in the entoderm and migrate into the mesenchymal zone of the germinal ridge where the surrounding mesenchymal cells differentiate to form primordial follicles. According to Fischel's concept, the power of forming an organ (ovary) is originally possessed by the mesenchymal cells in a large area, which is gradually restricted to a narrower field, which in turn ultimately becomes the gonad. However, the mesenchymal cells beyond this field retain a potentiality for differentiation, if stimulated to development. Variation in histological structure in granulosa cell tumors is probably dependent upon the stage of differentiation in the tumor cells toward the adult granulosa cell form. This explains why, in the words of Schiller, "the tumors when unripe have the character of connective tissue and when ripe show epithelial structure." Thus, undifferentiated but potentially specific granulosa cells may remain in the territory originally occupied by the genital fold. In the adult, this zone extends retroperitoneally from the region of the adrenal to the cortex of the ovary. It is in this area that extraovarian granulosa cell tumors may be expected to occur.

All of the foregoing statements and case reports, then, are in support of the theory of embryonic cell rests or ovarian mesenchyme as the origin of these tumors.

2. The second theory, that of Robinson, claims that primary ovarian cancers (in which he includes granulosa cell tumor) arise from epithelial elements which constitute part of the fully formed sex gland; i.e. from the granulosa of the graafian follicles. He presents histopathological findings which are stated to show the gradual transition of granulosa cells of a graafian follicle to a fully formed granulosa cell tumor.

In support of this theory, Butterworth has made observations on the histogenesis of ovarian tumors produced in mice by x-rays. After irradiation, the ova and many of the large follicles degenerated and disappeared. Smaller follicles, however, apparently were not affected. These nests of cells seemed to increase slowly in size. Eventually, they proliferated more rapidly and invaded the surrounding stroma, forming granulosa cell tumors. This, then, is direct observation of an experimental production of granulosa cell tumors.

The majority of opinion, however, is in favor of the embryonal cell origin of these tumors.

MORBID ANATOMY

The descriptions of the gross and microscopic appearance of granulosa cell tumors are numerous. According to Dockerty and MacCarty, 90 per cent are unilateral and 90 per cent are solid. They vary in size from pin head nodules to the large retroperitoneal tumors reported by Voight and the 34 pound tumor described by Te Linde. Grossly, they usually appear well encapsulated. They are smooth, firm, and not adherent to the

surrounding structures. On cut section, they may be partly solid and partly cystic. The cut surface may be bright yellow similar to a corpus luteum or it may have a fleshy appearance like sarcoma. Microscopically, three types are usually described: folliculoid, cylindroid, and diffuse. The folliculoid form appears most differentiated and most closely resembles adult granulosa cells, with follicle formations. The cylindroid type is somewhat less well differentiated, the tumor cells appearing in columns or strands, between the surrounding fibrous stroma. The diffuse form is the least differentiated and is the most difficult to distinguish from a malignant ovarian neoplasm of other origin. It is usual to find areas which are more or less characteristic of any or all of these types in the same tumor. This is in accord with Robinson's statement that these tumors in the course of their evolution present different phases of growth which are not entitled to separate classifications. The so called "types" then are only various phases of a single tumor.

Pratt, in an excellent article on this subject, gives a more complete description of the morbid anatomy of granulosa cell tumors.

QUESTION OF MALIGNANCY

This is the phase of the subject in which we are most interested, because we believe our case is definitely a representative of the malignant granulosa cell tumor. Dockerty and MacCarty consider that 90 per cent are of a relatively low grade of malignancy. On the other hand, Novak and Brawner (18) state that "the degree of malignancy is considerably greater than we would gather from most authors, many of whom speak of these tumors as relatively benign." They were of the opinion that 9 of their 33 cases showed unmistakable evidence of malignancy, on the basis of the picture at operation and recurrence. This would put the clinical malignancy rate at 28.1 per cent. Te Linde states that the majority of these tumors are relatively benign but malignant forms occur (5 to 10 per cent).

The diagnosis of malignancy may be suggested by the microscopic picture, by the fact that recurrences are found, and by the demonstration of actual metastases.

Structurally, these tumors occupy a middle position as to malignancy. They are usually well encapsulated grossly and are nonadherent. Microscopically, however, the cells may be found invading the rather dense capsule and mitoses may be fairly numerous. Te Linde found mitoses most often in the small tumors, which therefore appeared more active than the large ones in which there was more fibrosis and degeneration. Pratt states that, when malignant, they are more often bilateral. Other authors do not make this statement. They must be differentiated from other types of primary or secondary ovarian carcinomas. It may be, as Pratt says, that the differential diagnosis of malignant granulosa cell tumors will eventually depend upon whether or not the hormone estrin can be elaborated by the malignant tumor cells. That malignant tumors of endocrine glands may be able to produce hormones which are the same as, or comparable to, those formed by the normal gland is suggested by cases of carcinoma of the thyroid gland with hyperthyroidism (Eiselberg). Also, according to Bard's dictum, as quoted by Schattenberg and Harris, it is stated that certain tumors continue to produce the physiological secretions of the parent tissues from which they arose. We believe that our case also supports this contention, as will be seen later.

Schiller is in favor of a guarded diagnosis of malignant granulosa cell tumor on the basis of histological structure alone, since differentiation from other malignant ovarian tumors is difficult.

Robinson presents 4 points of difference from other carcinomas of the ovary: (a) uniformity of the proliferating epithelium, especially early; (b) absence of mitoses with rare exception; (c) absence of infiltrative and destructive tendencies; (d) spread of the tumor by continuity and extension, not by the lymph or blood streams. We cannot agree with all of these statements. It is clear, however, that the microscopic picture is certainly not one which allows for a positive diagnosis of malignancy.

Recurrences are more tangible, clinical evidence of possible malignancy. Various figures are given as to the rate of recurrence. Instances of recurrence are reported by Rummeld, Bland and Goldstein (3), Klaften, and Szathmary. According to the latter two, recurrences occurred in 5 per cent and 10 per cent of cases, respectively. In the cases of Rummeld and of Bland and Goldstein (both in children), no recurrence took place after the second removal. Schiller suggests that these "nonmalignant recurrences" are to be regarded rather as newly formed and independent tumors of the same type as the primary tumor.

The reports of descriptions of actual metastases are not numerous. Of Klaften's 80 cases, 7.5 per cent were "inoperable" when first seen. The usual sites for metastases are peritoneum, omentum, and broad ligament. Bell and Datnow present a photomicrograph of a metastatic area in the omentum from Dodd's case of granulosa cell

tumor. The ovaries were not removed in this case, however. Another of their patients died of "general peritoneal dissemination"—no further description is given. In still another of their cases, miliary metastases were found scattered throughout the body and cervix of the uterus.

Metastases may also be to more distant structures. Soltmann reported a case of bilateral granulosa cell tumor of the ovaries in a 41 year old woman, who died of an ileus 10 days after the removal of the tumors. At autopsy, metastases to the first and second sacral vertebrae were found. Klaften encountered a case of a 9 year old patient who died 1 year after operation with metastasis in the brain.

One other feature concerning metastases is that they may occur very late; i.e. 3 to 21 years after removal of the primary tumor (Kleine). Klaften, suggests, therefore, that the primary tumor inhibits the formation of distant metastases in the same manner as mature follicles and corpora lutea appear to inhibit the maturation of other follicles in a normal ovary. It is obvious, then, that these cases must be observed over long periods of time before a statement as to absence of metastases can be made with certainty.

CASE REPORT

Our case is one of a 65 year old white woman who was admitted to the Charity Hospital on October 16, 1941 in a semistuporous condition. During the previous night, she had apparently suffered from a "stroke." She was a known hypertensive of some duration. No history referable to the possible occurrence of vaginal bleeding, etc. was obtainable. On physical examination, the blood pressure was 280/130. She was a well developed, well nourished white woman who appeared to be about 65 years of age. She was in a semiconscious state. Pupils were small and fixed. Breasts were atrophic. The heart was enlarged to the left; a systolic thrill was present over the precordium and a systolic murmur was heard here. Râles were present at both lung bases and the liver edge was palpable. A small amount of fluid was thought to be present in the abdomen. Pitting edema of both lower extremities was noted. There was a flaccid paralysis of the entire left side of the body. She was in a moribund state, and died 2 hours after her admission to the hospital.

The clinical diagnosis was: (1) hypertensive cardiovascular disease; (2) cerebrovascular accident.

Necropsy was performed. The peritoneal cavity contained about 50 cubic centimeters of clear serous fluid. About 200 cubic centimeters of slightly sanguineous fluid was present in each pleural cavity. The heart weighed 610 grams. There were only 2 cusps for the aortic valve, both showing marked calcification. The lungs were congested. The spleen and liver revealed evidences of passive congestion. On the ileum, about 4 feet from the ileocecal valve, there was a white, firm plaque which measured approximately 1 centimeter in diameter. Other smaller grayish white areas were seen on the serosal surface of the terminal ileum. These averaged approximately 2 millimeters in diameter. The adrenal glands showed no gross evidence of pathology. The kidneys were small, pale, and granular. A few infarcts measuring 1 to 2.5 centimeters in diameter, were present in the right kidney. This kidney was freely movable, being poorly attached to the posterior body wall.

The uterus did not appear enlarged. It measured approximately 8 by 3 by 1.5 centimeters. On cut section, the myometrium was about 1 centimeter thick. The endometrium was yellow to purple in color and somewhat velvety in appearance. A polypoid structure, measuring 1.5 centimeters in diameter, was attached to the endometrium in the fundus. A smaller polyp was attached to the endometrium in the midportion of the body of the uterus. The fallopian tubes were of normal length but the diameter was diminished. They each measured 5 centimeters by 3 millimeters. The right ovary was slightly larger than the left. The right ovary measured 3.5 by 2.5 by 1 centimeter; the left approximately 2.5 by 2 by 1 centimeter. On cut section, there was noted in the right ovary, a firm, round yellow structure, measuring 1.4 centimeters in diameter. Corpora albicantia were present in both ovaries. The cut surface of the left ovary showed nothing of significance.

The brain showed evidence of edema and congestion. The pituitary gland was not enlarged. Its cut surface showed nothing of note. The liver presented no gross abnormalities.

On microscopic examination, the kidneys showed evidence of both chronic glomerulonephritis and nephrosclerosis. There was calcification of some of the smaller vessels in the kidneys. The liver showed an increased amount of fibrous tissue in the portal spaces and also evidence of passive congestion. There was hypertrophy of the heart muscle. Serial sections of both adrenal glands were studied, but revealed no evidence of tumor growth or other pathology.

The sections of the yellow nodule of the right ovary (Figs. 1 and 2) presented a distinctive tumor, composed of many rather large cells. These cells showed only slight tendency to form "rosettes." Only a few mitoses were seen. Many of the nuclei contained dark eccentric nucleoli. These tumor cells were surrounded by a rather dense zone of fibrous tissue, but, nevertheless, appeared to be invading this capsule.

Sections through the largest nodule on the ileum showed many collections of the same type of cells noted in the tumor of the right ovary. Here, however, the cells showed very definite tendency to be grouped into "rosettes" and appeared to be attempting to form small follicles—Call-Exner bodies—(Fig. 3). These collections of cells were most prominent in the subserous and submucosal layers, but were present in all coats of the intestine in this area. The mucosa here was necrotic, no nuclei being present.

In the section of uterus, the myometrium was thickened, with hypertrophy of the individual fibers. The endometrium (Fig. 4) was also thickened and showed an appearance which was quite typical of the "Swiss cheese" pattern. The sections of the left ovary showed nothing of note.

The pathological diagnosis was (1) chronic glomerulonephritis and nephrosclerosis, (2) hypertrophy and dilatation of the heart, (3) cerebral edema, (4) malignant granulosa cell tumor of right ovary with metastases to the terminal ileum, (5) generalized arteriosclerosis.

We believe, of course, that the granulosa cell tumor in this case was an incidental finding, the cause of death probably being a combination of cerebral edema and cardiac decompensation. The diagnosis of granulosa cell tumor in this case is based upon the gross and histological structure and upon the finding of a hyperplastic, proliferative endometrium in a senile woman. That the

tumor was malignant is shown by the metastatic area in the ileum, and by the mitoses, anaplasia of cells, lack of differentiation and tendency to invasion seen histologically.

Probably the feature of greatest singularity in this case is the degree of differentiation of the cells in the metastatic area. Here, the resemblance to a well differentiated folliculoid granulosa cell tumor is much more pronounced than in the rather diffuse, anaplastic pattern of the primary tumor. No similar description was encountered in the literature, although the metastatic lesion in the omentum presented in the photomicrograph by Bell and Datnow does show a fairly well defined folliculoid structure. The ovaries were not removed in their case, however, and therefore the primary tumor is not described. Our report presents only a single case and therefore no definite conclusions can be drawn. However, a more highly differentiated histological pattern in the metastatic lesion than in the primary site suggests an explanation for the appearance of late metastases, such as were noted by Klaften (3 to 21 years). Being well differentiated, they are slow growing and, therefore, take a long time to become manifest. Another point which might be mentioned is that, since the cells in the metastatic area were more differentiated than those in the primary site, they are more likely to have had greater potentiality for hormone production. For those who object to conceding the capability of hormone production to a malignant granulosa cell tumor, there is offered an explanation whereby the more differentiated, and presumably the more benign metastatic lesion may be responsible for hormone production. We believe the presence of a hyperplastic proliferative endometrium in our case of a senile woman is rather definite and conclusive evidence of endocrine activity of the tumor. No normal follicular structures were seen in the otherwise senile, sclerotic ovaries.

Thus, this case appears to be one of definite malignancy in a granulosa cell tumor, which shows the special feature of marked differentiation or "reversion to type" in its metastatic site.

SUMMARY

1. The subject of granulosa cell tumors is discussed from the standpoint of history, occurrence, pathological physiology, histogenesis, and morbid anatomy.

2. The question of malignancy of these tumors is considered.

3. A case is presented in which a granulosa cell tumor of the right ovary with metastases to the terminal ileum was found at autopsy. There was evidence of endocrine activity, as manifested by the hyperplastic proliferative endometrium. The metastatic site showed an unusual feature in its marked degree of differentiation.

NOTE: A report by McCartney of another malignant granulosa cell tumor of the ovary has recently been called to our attention. In this case, at autopsy, there was seeding on the peritoneum and in the mesentery, and metastatic lesions in the mesenteric lymph nodes and brain. The patient was a 59 year old white female. McCartney, J. S., Jr. Arch. Path., 1940, 29:263-270.

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EXPERIENCE WITH 105 LEG LENGTHENING OPERATIONS

ALVIA BROCKWAY, M.D., and SAMUEL BENJAMIN FOWLER, M.D.,
Los Angeles, California

LEG lengthening operations have been done i n sufficient numbers that their indications, value, and shortcomings may be well understood. During the past 12 years we have done 105 such operations. These patients have been continuously followed and the end-results in over 80 per cent of the cases were available for critical analysis. The size of the series and the duration of the observation should make our experience worthy of report.

The original Abbott technique and apparatus have been used exclusively. While Abbott later reported an ingenious new technique based on more rational anatomical considerations, we have not adopted it. This is because it seemed to be rather radical with two extensive operations following closely together and because the original technique had given us satisfactory results. The only modification in our apparatus is that all four pins fit into a slot so that each pin may be independently manipulated when necessary to control bowing of the fragments. In most of our later cases we have used extraperiosteal dissection of the tibia, but our experience with this has not yet been complete enough to appraise its value in contrast to the subperiosteal approach.

The operation was most frequently done for shortening due to anterior poliomyelitis. It has also been done for a number of other conditions as will be noted from the table.

Relation to other reconstruction surgery. The poliomyelitis patient presents more of a surgical problem than other patients who face leg equalization surgery. This is because several other operations may be necessary or may have already been done. The sequence of the various surgical procedures is important.

If, as occasionally happens, the patient arrives a number of years after his illness and has had no surgery on the lower extremity, leg lengthening, generally speaking, should be the first step. Because of the tendency to bowing of the tibia and foot deformities, leg lengthening should preferably be done before any osteotomy to correct leg alinement, tarsal arthrodesis, or muscle transplant below the knee.

On the other hand, certain types of surgery should precede the leg lengthening operation. For example, hip contractures, hips arthrodesed in undesirable attitudes and unstable dislocated hips require attention prior to leg lengthening. Until the hip has been put in its permanent optimum position it is not possible to determine the needed length.

At what age should the short leg be lengthened? It was formerly our impression that once the legs of an anterior poliomyelitis patient were made equal they would so remain. Others have been of the same impression. This idea was based on the theory that the discrepancy in leg lengths was initiated during the acute and convalescent stages of the disease and was perpetuated and exaggerated by the unequal thrust on the two legs incident to weight bearing. We do not believe this to be entirely true and are of the opinion that the main factor is the paralysis itself with the generalized atrophic changes incident to it. At first we lengthened legs of many patients between the ages of 8 and 12. After the operation the legs apparently kept pace for a time, possibly due to the temporary stimulus of the surgical trauma or because the lower extremities were then in a period of relatively inactive growth. However, as these patients were followed through their growth period, we found that many of these legs dropped back from ½ to 1½ inches. The discrepancy was more marked in the younger patients with the more severe paralysis.

Legs that are lengthened before the end of growth, when the shortness is due to epiphyseal destruction as with tuberculosis, osteomyelitis, and fractures, obviously will not keep up with the normal leg.

The congenital short leg of 1½ to 2½ inches, once equalized, continued to maintain equality as did one case of congenital spastic monoplegia. The ages of the patients at surgery were 10, 11, 12, 14, and 16 years. All were observed to the conclusion of their growth without relative change in leg lengths.

From our experience we believe that leg lengthening should not be done until the period of rapid extremity growth is over. There are exceptions, however, and it is good psychology to remove the stigma of the ugly raised shoe as early in life as is feasible. Given a paralytic short leg in which the shortening is already as great or greater than

From the Clinics of the Orthopaedic Hospital.

one could reasonably expect to overcome by leg lengthening, there is no point in waiting and this for several reasons. This patient often needs other surgery which preferably follows the leg lengthening operation. Also the younger patients better tolerate the stretching of soft tissues and osteogenesis is more efficient. Legs in which the shortening is not due to paralysis may be lengthened at a comparatively early age. If the cause is related to epiphyseal destruction the lengthening must be accompanied by appropriate epiphysiodesis in the long leg.

How much should the short leg be lengthened? To determine the shortening we measure the legs with a tape and by leveling the pelvis with a raise. Finally the clinically leveled pelvis is checked by a standing x-ray film. Pelvic obliquity, the relation of the femur to the pelvis, leg malalinement and fixed equinus deformity of the foot may make these measurements misleading. It is surprising how much functional length the equinus deformity of an astragalectomized foot adds to the leg. If it requires 2 inches under the heel of a male patient to permit weight bearing on both the heel and metatarsal heads, then this deformity adds 1 inch of functional length if the patient wears a 1 inch heel. With women wearing a higher heel the added length is less. A trial with a raised shoe to determine the optimum lengths needed is always preferable and is mandatory when hip function is impaired.

In cases of anterior poliomyelitis, the two legs should not usually be made the same length. How much shorter the short leg should remain will depend upon the severity and the location of the paralysis. With a weak hip and knee it is better to leave the leg about ½ inch short. When the paralysis is confined to the foot and ankle the legs may be equalized.

When there exists a fixed scoliosis, leveling the pelvis may aggravate the curvature and cause pain. In instances of this sort, as in cases of fused or unstable hips, it is imperative that, before surgery, performance with a shoe raise be studied.

Tibial versus femoral lengthening. Lengthening below the knee has been the preference of most surgeons and in our series only 9 lengthenings were done in the femur. Six of these were classified as poor results constituting almost half of our total of poor results. In our limited experience with femoral lengthening we have found the bone fragments harder to control, union slower, and the knee joint difficult to mobilize because of the traumatic arthritis in the joint itself and to adhesions in the extensor apparatus. Immobilization in a spica cast is much more confining than the long leg cast necessary when the lengthening is done below the knee.

The patient's viewpoint. It has been our policy not to bring pressure to bear on the patient confronted with the possibility of leg lengthening. When such an operation seemed advisable, the operation was explained to the parents and the patient, and the final decision was made by them. It is interesting that a large number of patients came in voluntarily and asked to have the surgery done after talking with others who had already gone through with it.

This fact indicates how strongly most patients feel the stigma of wearing a heavy raised unsightly shoe. Not only is such a shoe a never ending source of expense, a dead useless weight attached to the end of a weak leg but even more important, and something some surgeons do not sufficiently realize, it is the badge of the cripple and the psychic trauma it must cause is evidenced by the fact that so many ask to have the operation performed, even though they know that such treatment requires weeks of hospital care and months before the leg is well and strong.

RESULTS

In 65 per cent of the cases the results were excellent.

In 22 per cent of the cases the results were good in that the preplanned length was obtained with an ultimate strong, useful limb. In this group were delayed unions, long continued drainage with or without sequestration, bowing of the tibia, foot and knee deformities. Likewise included are cases in which the leg lengths were equalized but did not so remain.

In 13 per cent the results were poor in that the length obtained was inadequate or that the patients had residual deformities not readily amenable to treatment.

In the average case (excluding 7 in which no length was obtained) lengthening was started on the fifth day and continued at the rate of 1 to 1½ millimeters per day until the preplanned length was obtained. A long leg cast was applied at 11 weeks after operation and the pins were usually removed. Plaster fixation was discontinued 24 weeks following surgery, and at the end of 8.9 months weight bearing without support was begun. This meant that there was generally noted x-ray roentgenographic evidence of union prior to this. There was no appreciable difference in length obtained between the paralyzed and nonparalyzed legs.

Bony union was complete in 30 months in 100 per cent of the cases, 24 months in 96 per cent of

TABLE I.—LEG LENGTHENING OPERATIONS[1]

	Operations
Dislocation congenital hip	7
Dislocation traumatic hip (epiphyseal injury)	1
Purulent arthritis hip	4
Fracture femur	1
Fracture hip with malunion	1
Fracture tibial epiphysis	1
Hemiectromelia	4
Osteochondritis, hip	1
Osteomyelitis, femur (with epiphyseal involvement)	3
Paralysis spastic hemiplegia, cerebral	1
Poliomyelitis anterior, residual effects	62
Short leg, congenital	6
Talipes equinovarus	2
Tuberculosis hip	6
Tuberculosis knee	4
Volkmann's ischemic myositis	1
Total	105

[1]As of October 29, 1941.

TABLE II.—GENERAL STATISTICS

Average lengthening obtained, 1.8 inches

Age groups	Per cent
Under 12 years	18
12 to 18 years	64
Over 18 years	18

Time to complete bony union	Per cent solid
30 months	100
24 months	96
12 months	80
9 months	57

the cases, 12 months in 80 per cent, and 9 months in 57.3 per cent.

COMPLICATIONS

The complications that have been encountered in this series of leg lengthenings have been many. Both their incidence and gravity can be lessened. This can, we believe, be better accomplished by diligent and understanding postoperative care than by more radical surgical techniques and complex types of apparatus.

The original Abbott technique has been closely followed. The dissection consists, briefly, of the usual Z osteotomy of the tibia, oblique osteotomy of the fibula, section of the fascia and interosseus membrane, and lengthening of the tendo calcaneus except when paralyzed. Every effort is made to denude the tibia as little as possible. This is a relatively conservative dissection, but it will yield 2 inches of length handily. There is a strong tendency to bow, but it is probably significant that in over 100 cases there have been no deaths, no amputations, and no nonunions.

The lengthening apparatus is modified only in two respects. The four pins fit into individual slots allowing an anteroposterior excursion of about 1 inch. This is often insufficient to control bowing, so the extension bars are made of soft steel which can be easily and accurately bent with the bending irons. The fact that this has been done in more than half the cases reflects something of its value to us.

Absolute control over the bone fragments is extremely important. Laxity here leads to the familiar sequence of bowing and separation of the bone fragments, necrosis of the skin, aseptic necrosis or low grade osteomyelitis (13 cases), sequestration (11 cases), delayed union, and genu or pes valgum. However, if one is diligent in observation and understands the problem, he can persevere in the face of these difficulties to obtain adequate length and finally obtain a good end-result.

At the time of surgery one real hazard is fracture of one of the bone tongues, and this occurred four times in our series (of which two were in the femur) and prevented trying for any length. In one case the upper fibular fragment was inadvertently penetrated by a lower pin and had to be replaced when later discovered. In another case the fibular fragments locked one on another and had to be disengaged.

One severe postoperative infection was encountered in which no lengthening was obtained and one child of 7 years had a moderate postoperative infection with massive early callus formation which allowed only about one-half the desired length. There were several cases with mild infections such as a stitch abscess or infected hematoma which delayed the start of lengthening a few days, but thereafter proceeded without untoward event. A number of the cases showed drainage or even sequestration late in the lengthening process, but this was probably incident to aseptic necrosis in most if not all cases. Pin hole infections were annoying and were persistent enough to require curettage in 4 cases.

In several cases the fibula did not lengthen sufficiently. In 2 of the cases it pulled up, interfering with ankle stability and an arthrodesis was thought necessary. More commonly the head of the fibula pulled down. This occurred in varying degrees up to one inch, but in no case did it seem to cause any disability.

There were no permanent nerve palsies. In a similar manner the flexion deformities of the knees, feet, and toes surrendered to time and physiotherapy.

It was interesting that there were no cases of nonunion, even though many were long delayed. Table II is rather misleading in that it refers to weight bearing rather than to bony union by x-ray.

After seeing several of these lengthened tibiae, drawn thin by lengthening and fracture under slight provocation, we tended to be rather conservative about allowing unrestricted activity. Partial weight bearing was encouraged after danger of telescoping of the fragments was improbable. Distraction, infection, and increasing age appeared to delay union definitely. We are not sure that mild infection has any deterring effect on osteogenesis other than its interference with the local blood supply at the osteotomy site.

Fractures incident to full weight bearing occurred in 6 cases and in 5 the injury was trivial. The one due to a severe injury had had delayed union following femoral lengthening and immediate open reduction with a bone graft had been performed. In the other cases healing was without complications.

PRESENT STATUS OF LEG EQUALIZATION OPERATIONS

At the present time there are 4 proved procedures by which discrepancies in leg length may be overcome. Each has its advantages and while some rules can be laid down, in the final analysis, it will be the judgment of the surgeon that will be the deciding factor.

The first and oldest is amputation and prosthesis. While not popular at present, there are circumstances when it is to be highly recommended. A severe foot deformity coupled with marked shortening of the leg would be ideal for such a procedure, likewise a poliomyelitis victim with a good functional hip presenting severe paralysis of the knee, ankle, and foot in which shortening was severe.

The other methods to equalize leg lengths are shortening of the long leg, epiphyseal arrest, and lengthening of the short leg. At present the former two are in wider use. This is due to their undoubted advantage in many cases plus the fact that surgeons who are familiar with the shortcomings and difficulties of leg lengthening, may be too eager to turn to an operation of the complications of which they are not so uncomfortably aware.

Epiphyseal arrest. This is a valuable procedure and will be more useful as we learn more about growth. The surgery is relatively simple and the convalescence short. It has the disadvantage that fusion of the epiphysis may fail or be incomplete, leading to deformity. Likewise we are forced to apply a general rule of expected growth to a specific case, which may give far from the correct answer, particularly since the short leg may have pathology making the growth expectancy even more difficult of computation. Generally speaking, epiphysiodesis is indicated if: (1) the growth expectancy is compatible with the desired shortening; (2) the growth expectancy may be reasonably computed, both in the long and short leg; (3) it is desirable to combine it with either a leg shortening or leg lengthening operation, either due to severity of the paralysis or to match a destroyed epiphysis in the short leg.

TABLE III.—COMPLICATIONS

	Cases	Cases
Infections		
Severe immediate postoperative infection		1
Osteomyelitis or aseptic necrosis		13
Surgery to correct	11	
Persistent pin hole infection		6
Surgery to correct	4	
Ankle joint fusion		1
Bowing of tibia (over 20 degrees)		8
Surgery to correct	6	
Foot deformities		
Equinus		common
Moderately severe for long period with later spontaneous improvement		
Calcaneus		1
Valgus		2
Peroneal nerve palsy		2
Both eventually recovered		
Fibular detachment		
Head of fibula pulled down but no functional disability: varying degree in at least		12
Distal end fibula pulled up:		
Probably will require ankle fusion		2
Delayed union (over 12 months)		17
Fracture of bone tongue at surgery		4
1. Femoral	2	
2. Tibial	2	
Late fractures		6
Miscellaneous		
Loss of appreciable length due to premature removal pins and application cast		2
Inadvertent over lengthening due to spring tension of pins after lengthening stopped		3
Inadvertent drilling upper fibular fragment with lower tibial pin		1
One or more pins broke during lengthening		3
Failure to obtain any or very little length		7
Due to fracture of bone tongue at surgery	4	
Due to severe postoperative infection	1	
Due to inadvertent drilling of fibula	1	
Due to early massive callus formation	1	

Leg shortening. This is the most accurate of all leg equalizing operations and has a wider field of application. The gravity of such major surgery on a good leg is real, particularly if the short leg is of poor power or function. From our experience we prefer to shorten the femur in the subtrochanteric region, using rigid internal fixation. It is a desirable procedure: (1) If the shortening exceeds 1½ inches. (2) After the growth of the leg is at or near completion. (3) If the short leg is a good functional member. (4) If the patient is of normal or above normal height.

Leg lengthening. This is a tried operation and has given results to make it worthy of perpetuation although its field of application has been lessened in the past few years. We consider it a sound procedure under the following conditions: (1) If the desired lengthening does not exceed 2¼ inches. (2) If the function of the short leg is too poor to risk surgery on the normal leg. (3) If the patient is in the age group between 12 and 25 years. (4) If bone and soft tissue are of good quality. (5) If the patient's stature is average or short. (6) If the patient refuses to have an operative procedure performed on the long leg.

CONCLUSIONS

During the past 12 years the leg lengthening operation has been put to a critical test. Tibial lengthening is a valuable procedure under proper indications. Femoral lengthening has been unsatisfactory. We are now doing more femur shortenings and epiphyseal arrests but do not think that they can supplant leg lengthenings.

Leg lengthening will always entail certain hazards and there will probably always be some poor results, but with the experience gained we feel that the hazards and poor results can be reduced to a creditable minimum.

A NEW APPROACH TO THE DIAGNOSIS OF HERNIATION OF THE INTERVERTEBRAL DISC

WILLIAM DUNCAN, M.D. and THOMAS I. HOEN, M.D.,
New York, New York

THE earlier experiences in this hospital[1] in the treatment of herniation of the intervertebral disc were similar to those in many other institutions in that the results were inconsistent and frequently unsatisfactory. Accepted diagnostic methods were employed routinely and much dependence was placed upon neurological and myelographic findings. An analysis of our results indicated clearly that too much reliance upon these criteria had frequently led us into error.

During the past year, a new diagnostic approach has been employed with consistently satisfactory results. This approach is based chiefly upon a study of alterations in both the attitude of the lower spine and mobility of the intervertebral joints, and we have come to recognize a syndrome which we believe to be pathognomonic of the disease in question. We have been able, not only to detect the presence of a herniation, but to predict its level and placement in relation to the midline. This is of great value in directing and reducing the extent of the subsequent operative procedure.

In this preliminary report, we present the use and rationale of these diagnostic methods. A general review of the subject and historical study may be found elsewhere (4).

To present our concept of the pain mechanism on which these diagnostic methods are based, certain anatomical and pathological considerations are necessary. The monograph of Beadle, a student of Schmorl, contains an excellent description of the normal and pathological intervertebral disc, and his work has aided us in correlating physical findings with pathological conditions.

The normal disc is a fibrocartilaginous cushion between the cartilaginous plates of the vertebral bodies. The outer portion of this disc is composed of concentric laminations of dense fibrocartilage, which, on fresh section, are shown as discreet circular rings—annulus lamellosus (Fig. 1, *b*). Centrally, these cartilaginous rings blend imperceptibly with the nucleus pulposus (Fig. 1, *a*).[2]

The nuclear tissue is a loose, semigelatinous mass of fibrocartilage with a fluid content greater than the annulus. This seems to account for its inherent elastic turgor. The unique feature of the system is its expansile resiliency, i.e., its ability to maintain separation of the vertebral bodies and to absorb the countless stresses and strains of normal activity.

Certain other structural features are worthy of note because they undoubtedly affect the course of pathological changes. The joint capsule, which herniations must distend or rupture, is relatively thin over the posterior aspect of the joint in the region of the neural canal. It is re-enforced in the midline, however, by the posterior collateral liga-

[1]Hospital for Special Surgery maintained by the New York Society for the Relief of the Ruptured and Crippled, New York.

[2]Figures 1 and 2 are taken from *The Intervertebral Discs* by Ormond A. Beadle, by special permission from His Majesty's Stationery Office.

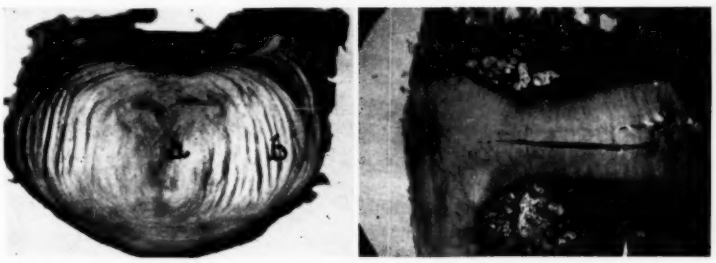


Fig. 1. Normal lumbar intervertebral disc shown in horizontal and sagittal section. Left, *a*, Nucleus pulposus; *b*, annulus lamellosus.

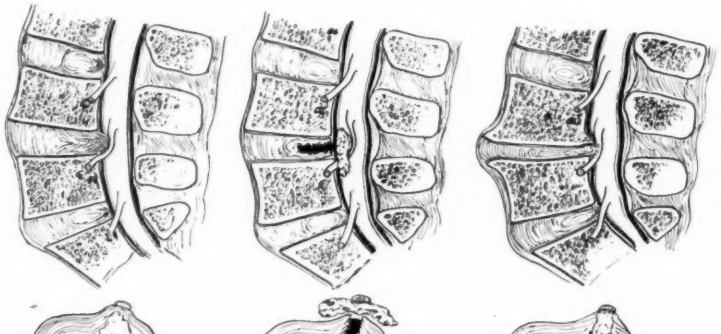
a b c

Fig. 2. Common pathological changes. a, Fibrillar degeneration of nucleus and inner annular rings; b, typical concentric tear of annulus; c, complete degeneration of entire nucleus and inner layers of annulus.

ment which probably accounts for the lower percentage of midline herniations. Another important consideration is the relative strength of the bony attachments of the laminated rings of the annulus: posteriorly these rings are more loosely attached than anteriorly, and consequently they can be more readily avulsed by a herniation. Furthermore, it is important to note that the disc itself has no blood supply and must absorb its nutrition from the cartilage plate. The fluid content of the nucleus diminishes with age and so must its elastic turgor. This loss impairs its ability to absorb trauma without local damage. Finally, it must be recalled that the intervertebral discs were primarily designed for flexibility, not the weight-bearing of the upright posture. It is not surprising then, as Schmorl has pointed out, that the intervertebral disc is one of the first tissues in the body to degenerate with age and usage. Thus, from an anatomical, physiological, and phylogenetic standpoint, the intervertebral disc endures a rather precarious existence.

PATHOLOGICAL EVENTS

Several types of pathological changes may occur within the disc (2). Fibrillar degeneration of the nucleus and inner lamellar rings (Fig. 2, a), simple concentric tears (Fig. 2, b), as well as complete degeneration of the entire nucleus and large areas of the annulus (Fig. 2, c) have all been described at length and need only be mentioned here.



a b c

Fig. 3. Three common types of herniations. a, Simple reducible herniation with intact capsule; b, complete extrusion of sequestrum through ruptured joint capsule; c, advanced type with narrowing of disc, bony proliferation, and fibrosis involving involved nerve root.

Fig. 4. Advanced type of herniation as in Figure 3 c. Note bony proliferation within the distended posterior joint capsule.

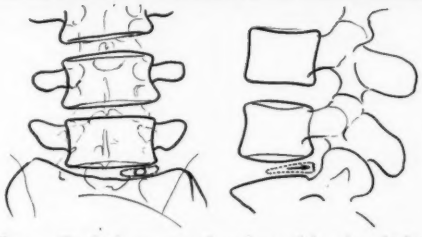


Fig. 5. Typical posture of patient with a herniation of the intervertebral disc between 5th lumbar and sacrum on the right side. Note the list to the left and the flattening of the lumbar curve.

Once these pathological changes occur, the intervertebral system loses its elastic resiliency and is consequently unable to maintain normal separation of the vertebral bodies. The volume of the disc has not been altered, only its turgor. As the disc collapses under body weight, the nonresilient, fragmented fibrocartilage is squashed as a semifluid mass, either into the vertebral body (Schmorl's node) or toward the periphery of the joint, there to invade the laminations of the annulus and bulge or rupture the relatively thin posterior capsule. Once this collapse occurs, a balance is restored between the volume and the remaining resiliency of the disc. The herniation has, so to speak, decompressed the disc temporarily. Further degeneration of the disc entails more loss of resiliency, more collapse, and consequently more extrusion of débris into the herniation. These posterior protrusions often impinge upon regional nerve elements, angulating, stretching, or actually pinching the involved nerve (the overlying lamina or ligamentum flavum acting as the other jaw of the pincer), thereby producing segmental pain, paresthesia, or paralysis.

In our experience, three types of herniations are encountered at operation. While quite distinct in individual cases, they probably represent only stages in a natural sequence. First, there is the simple herniating mass of fragmented cartilage and degenerative nuclear material distending the intact posterior capsule (Fig. 3, a). At operation, this appears as a tense, rounded bulge of the posterior capsule having the consistency of a tennis ball. When the thin capsule is incised, the fragmented cartilage either extrudes spontaneously or can be delivered by traction. In the second type, the joint capsule has been ruptured and the cartilaginous sequestra have migrated into the extra-

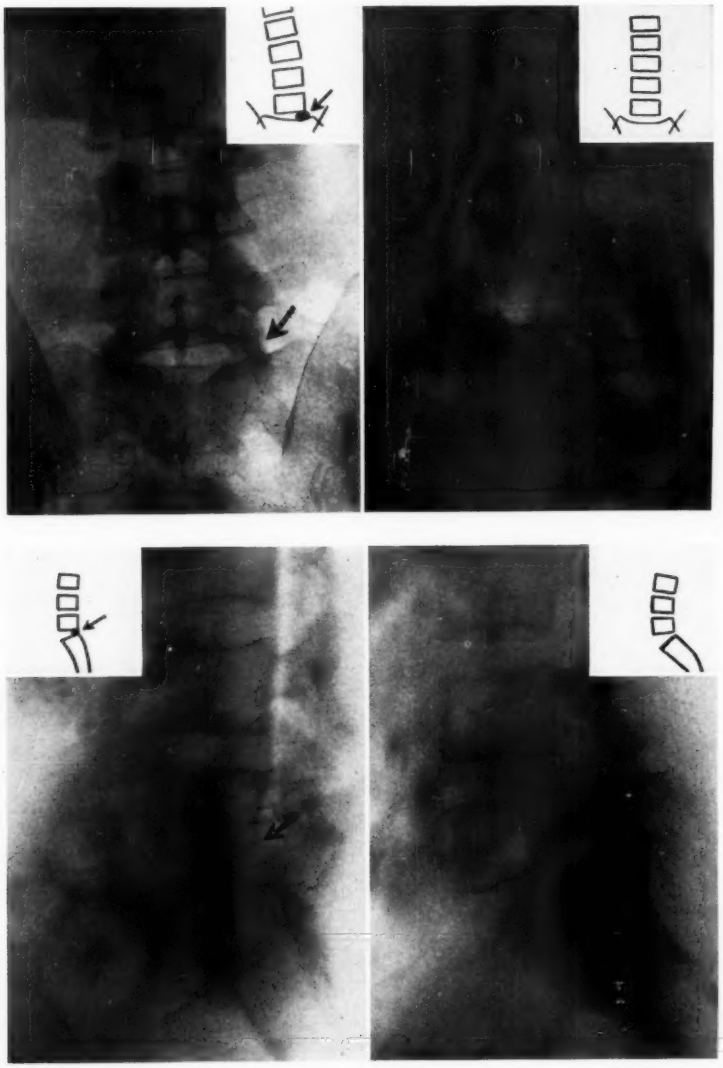


Fig. 6. a, above, Preoperative and b, postoperative views demonstrating the prompt restoration of posture following operative removal of disc protrusion and cartilaginous sequestra.

dural space (Fig. 3, b). Finally, the third type is characterized by fibrous fixation of the protrusion and involved nerve elements and frequently bony proliferation within the joint capsule (Figs. 3, c and 4). This may occur in either of the two previously mentioned groups, and probably represents a late stage in the pathological sequence.

The clinical behavior, especially the response to rest in bed, has often been so distinct in each of these three groups of cases that we have frequently been able to predict the type of herniation subsequently found at operation.

The first type with the simple bulging of the intact joint capsule has almost always responded

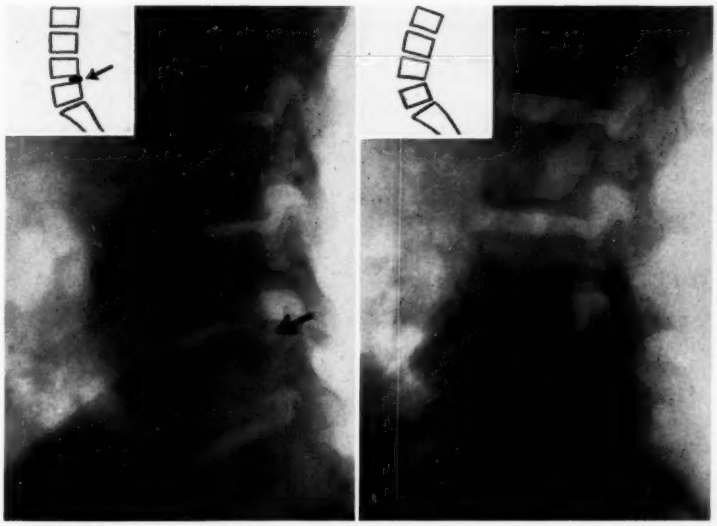


Fig. 7. a, left, Preoperative, and b, postoperative views, showing restoration of lordosis in a patient who had a herniation removed from the disc between 4th and 5th lumbar vertebrae.

well to complete bed rest. Usually within a few days there has been a striking relief of pain. So much so, that in our opinion this readily reducible "fluid type" of herniation should be given a trial of conservative treatment to allow the herniation to become fixed in a position which does not involve the nerve roots. The latter two types have, for the most part, shown little or no improvement with bed rest.

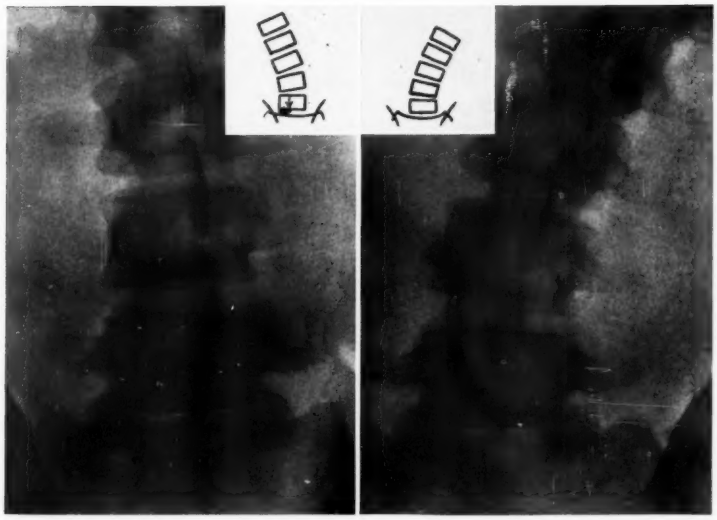
DIAGNOSIS

A patient with a herniation of an intervertebral disc really suffers from two lesions: a traumatic neuritis of the involved root or roots, and a diseased intervertebral joint. Since the neurological manifestations are much more obvious than the disturbance to the mechanism of the intervertebral joint, attention has been focused on the traumatic neuritis associated with this lesion, and the disease in the joint itself seems to have been overlooked. As might be expected, a uniform type of lesion of the intervertebral disc produces a uniform alteration in the mobility of the involved joint. This disturbance of joint mobility has been so consistent in our disc cases that we have come to recognize a definite syndrome on the basis of which the diagnosis and preoperative localization of the lesion has been possible.

The attitude of a deranged joint is usually determined by two factors; the mechanical limitation within the joint itself and the position of maximum comfort. How do these criteria apply to the typical postural deformity of a disc protrusion, i.e., the attitude of flexion of the spine and list away from the side of pain?

The intensity of peripheral pain or paresthesia is proportional to the force of the herniation against the involved root or roots. This forceful extrusion of the herniation depends entirely upon the amount of compression of the diseased or sequestrating area of the disc. Thus a patient with a disc protrusion faces the problem of transmitting the body weight along the spinal column without compressing the diseased area of the disc, thus avoiding further extrusion of the cartilaginous débris along the course of the herniation. To do this, one must tilt the spine away from the involved area of the disc. This posture entails a list of the spine away from the side of the lesion, and, since the mass is extruding posteriorly, an attitude of forward flexion is assumed (Fig. 5).

If the lesion is laterally placed in the intervertebral space, the prominent spinal deformity will be a lateral list, while in a more centrally placed protrusion, the outstanding postural deformity will be a flat back or a kyphosis due to flexion of the spine. Usually the two deformities appear in combination. The predominance of one or the other indicates the placement of the lesion within whatever disc may be involved.



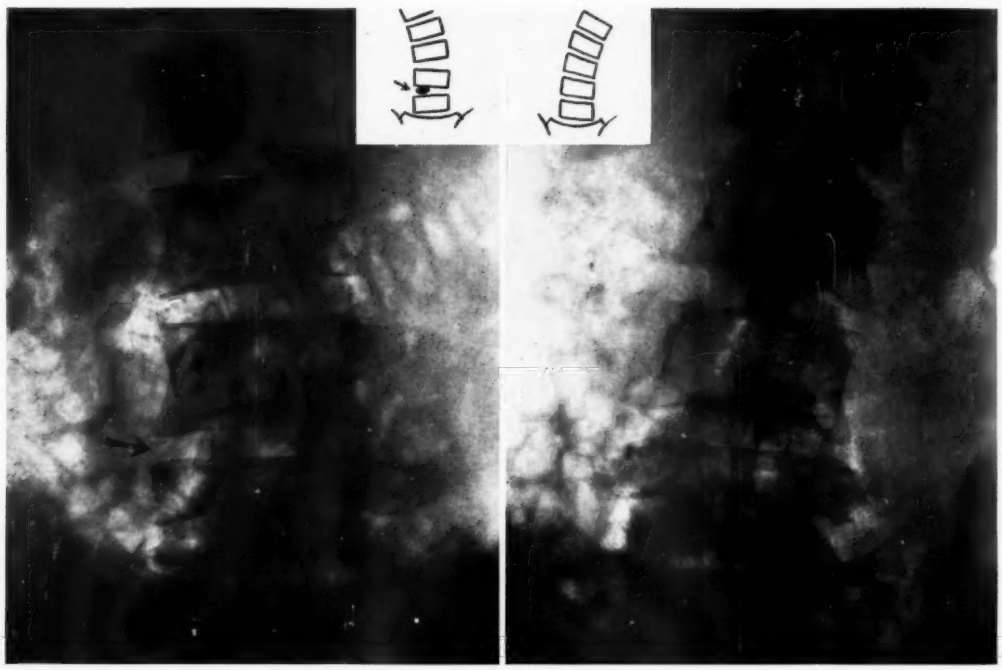


Fig. 8. a, above, Preoperative views of lateral bending to right and left showing diminished mobility of the involved joint, particularly on the side of the lesion. Note that when the patient bends to the side of the lesion (right) the lumbosacral disc fails to compress as do the discs above, while on bending away from the lesion (left), the disc shows a more normal mobility. b, Another patient demonstrating block between 4th and 5th lumbar vertebrae on right side.

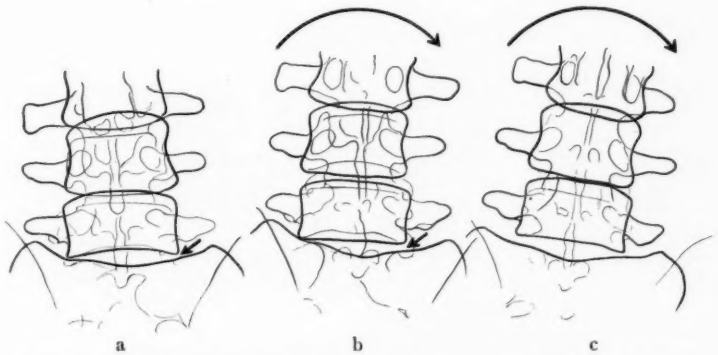


Fig. 9. A series of tracings made from films of a patient who had a herniation removed from the right side of the lumbosacral joint. Note how the herniating sequestrum (arrow) tilts the normal standing posture, a, and obstructs lateral flexion of this joint, b. The postoperative bending view, c, indicates restoration of mobility within this joint.

It has been noted that after a time, the spinal deformity apparently becomes fixed. Even during the occasional remission of symptoms and under anesthesia sufficient to permit complete muscle relaxation, the deformity is unchanged. We believe this fixation of postural deformity to be due to the presence of noncompressible cartilaginous sequestra within the diseased area of the joint. As stated one characteristic of a degenerating disc cartilage is its loss of resiliency. Like the fragments of a bucket handle tear of a meniscus of the knee joint, these sequestra naturally migrate to the roomier portions of the intervertebral space which have been opened up by the protective tilting of the spine and there act as a mechanical obstruction to the mobility of the joint. Comparison of films taken before and shortly after operation reveals a striking restoration of posture once the sequestrum has been removed (Figs. 6 and 7).

Realizing the diagnostic implications of the presence of a mechanical derangement within the involved intervertebral joint, we have attempted to visualize this feature more clearly by taking special bending films of the patient in lateral flexion to both sides and in forward flexion and extension. In the majority of our cases, these films have demonstrated a lack of spinal mobility localized to the involved joint. On the involved side, the joint may fail to narrow as much as the joints above and below or may even remain wedged open. Bending to the painful side usually demonstrates little, if any, resiliency within the affected joint (Fig. 8). (These films are best obtained with posteroanterior views of the patient standing, bending as far to each side as possible. The tube should be centered over the upper lumbar area and tilted caudally 15 to 20 degrees. This will allow good visualization of all the lumbar and some of the dorsal interspaces.)

Lateral views of the spine with the patient in extreme flexion and extension may also demonstrate a mechanical obstruction in the posterior aspect of the joint which will be apparent in the view in extension. The involved disc will fail to allow extension as do the joints above and below. It should be emphasized that these "bending

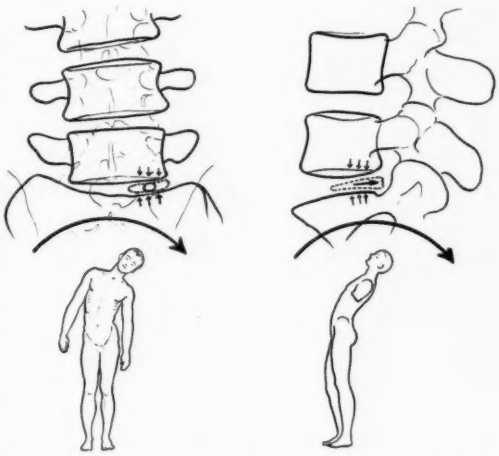


Fig. 10. Pain mechanism. Diseased cartilage and herniation are indicated by dotted lines. Arrows indicate the mechanical forces that are compressing the diseased area and thereby extrude the herniation against the root.

films" serve primarily to establish the level rather than the presence of a disc protrusion.

Postoperative bending films demonstrate clearly that once the sequestrum has been removed from the involved joint there is immediate restoration of joint mobility. This we feel is definite confirmatory evidence as to the exact nature of the preoperative obstruction in joint mobility (Fig. 9).

A careful study of the mobility of the spine will materially aid in the diagnosis and localization of a disc protrusion. One must not rely on an examination of patient in the standing position as it is as inaccurate as would be the determination of range of motion in a painful knee during weight bearing. The examination to determine the mobility of the intervertebral joint must be made with the patient in a recumbent and relaxed position. The various motions, i.e., forward flexion, extension, lateral flexion, and rotation can then be evaluated without the antagonism of the trunk musculature.

In our cases of disc protrusion, the only two consistently painful maneuvers have been lateral flexion toward the side of pain, and hyperextension. From what has been said before, it is obvious that these are the two motions most likely to compress mechanically the degenerated area within the disc and thus further extrude the herniation against the nerve root (Fig. 10).

Pain on hyperextension or lateral flexion is due to compression of the diseased area of disc. A latent period between the execution of the maneuver and the onset of peripheral pain has been frequently noted and this latent period, which may vary from a few seconds to a minute, represents to us the time required for the semifluid cartilaginous débris to be compressed along the path of the herniation. Following the latent period, the ensuing pain rapidly increases in intensity to a point where it can no longer be tolerated. In order to evaluate the effect of hyperextension and observe the latent period and rising tide of pain, a special maneuver has been used (Fig. 11). In this maneuver, the patient is supine and the knees are allowed to flex over the end of the examining table, thus producing a definite increase in the lumbar lordosis. The sacral and lumbar roots are thus completely relaxed due to the flexion of the knees and extension of the hips. Consequently, pain in these segments must be interpreted as due to pressure against, rather than traction upon, the nerve roots. In a typical case there is at first a latent period followed by a steadily rising tide of peripheral pain. If the painless extremity is flexed, the lumbar lordosis is reduced and there follows a prompt decrease in the pain. Flexion of both extremities on the trunk usually affords complete relief of pain and indeed is often the position of greatest comfort for the patient. A similar, though rarely so dramatic, a maneuver, has been used to elicit pain on lateral flexion of the spine (Fig. 12).

Upward pressure on the painful leg with traction on the painless leg will produce a definite lateral flexion of the spine toward the painful side. Here again, after a latent period, increasing pain may be experienced by the patient. The laterally placed lesion will be most effectively compressed by lateral flexion of the spine, while a more central herniation will be extruded by hyperextension. Thus, both the postural deformity and the painful spinal motion give indication of the placement of the herniation within the involved disc.

Other spinal motions, that is, forward flexion, rotation, or lateral flexion away from the side of pain, have been consistently painless. As such they represent important differential signs which will be spoken of later.

NEUROLOGICAL FINDINGS

The traumatic neuritis caused by disc protrusion is often the most prominent symptom of this condition. However, in our experience the neurological findings cannot be relied upon to differentiate or to localize the lesion. Like the Naffziger and other tests, these findings are confirmatory evidence to help complete the clinical picture. The precise localization of the level on the basis of segmental pain or paresthesia has proved hazardous, and we have seen the 5th lumbar root compressed by a laterally placed lesion in the lumbosacral joint, while in other cases with identical symptomatology, the same root has been compressed by a more centrally placed herniation between the 4th and 5th lumbar vertebrae (Fig. 13).

Certain relationships between neurological signs and operative findings are worthy of note. Bilateral neurological findings, rectal and vesicle disturbances, all suggest a midline lesion. Unilateral involvement of more than one dermatome also indicates a more centrally located lesion. Unilateral involvement consistently confined to one segment is usually associated with a laterally placed protrusion.

ROENTGENOGRAMS

A pronounced narrowing of the intervertebral disc as demonstrated by routine roentgenograms has not been present in many of our cases. When present, it seemed to represent a later stage in the pathological sequence. As stated, perhaps

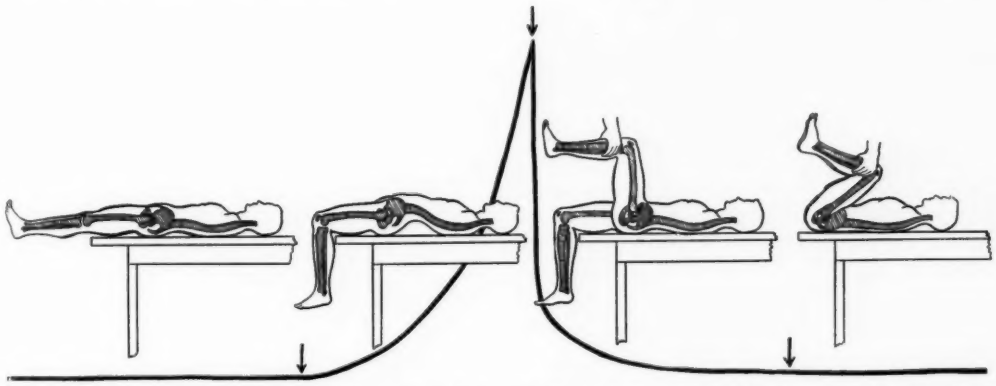


Fig. 11. A test used to evaluate the effect of extension of lumbar spine. Arrows indicate change of position. Note that as the legs are allowed to flex over the end of the examining table there is, at first a latent period followed by increasing peripheral pain. Flexion of painless extremity and then both extremities causes cessation of pain.

the most common finding is slight narrowing of the disc with tilting of the disc so that the intervertebral space is wider on the affected side.

Myelography by contrast medium has been reserved for those cases in which the pain, the posture, or the mobility of the spine suggested that the lesion was centrally placed, but did not establish the exact level of the lesion. It is also used in cases with extensive neurological findings to rule out tumors of the cauda equina, etc. In our experience, myelographic findings were consistently normal in laterally placed herniations.

DIFFERENTIAL DIAGNOSES

The initial enthusiasm attendant upon any proposal of a surgical cure for back pain has, in the past, led to unnecessary and fruitless surgery. Thus the various operative procedures, though quite satisfactory when indicated, have, one by one, fallen into disrepute. This should be borne in mind when making the diagnosis of a herniation of an intervertebral disc. Certainly, many cases of disc protrusion have been overlooked in the past, but from our observation we do not believe as others (1) that all patients with recurrent low midline or leg pain augmented by coughing and sneezing are suffering from a disc protrusion.

The following are common low back disorders which may closely simulate the lesion under discussion:

1. *The traumatic back* (*traumatic myofasciitis*). This condition is commonly met with in laborers following direct or indirect trauma to the muscles and ligaments of the back. As differentiating findings, they usually present lordosis, intense spasm of the erector spinae, and diffuse tenderness, especially over the muscle attachment around the posterior superior spine. They do not tolerate passive flexion of the spine and prefer an attitude of hyperextension. Increased local or radiating pain on coughing or sneezing is frequently present.

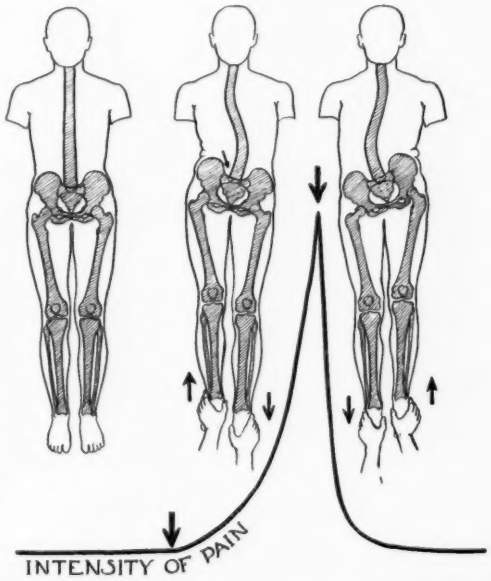
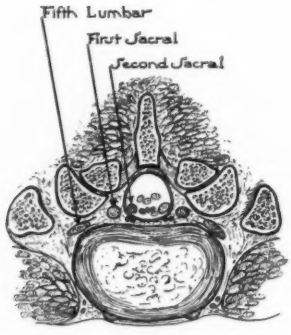


Fig. 12. A test for evaluating the effect of lateral flexion. With patient supine, upward pressure on painful extremity (right) and traction on painless extremity produces a pain response as plotted with heavy line. The reverse procedure causes cessation of pain.



a

Fig. 13. Drawings made from dissections of lumbar region show placement of nerve elements in relation to bony structure. Note how a single root may be involved at one of two levels and how at any one level one of two roots or the cauda equina may be involved.

2. Articular lesion. These cases are characterized by recurrent sudden attacks of low back and leg pain, often following a back twist or minor trauma. These may be due to a subluxation of one of the posterior articulations or sacroiliac joints, or a congenitally abnormal articulation. There is often an extreme postural deformity with a list and kyphosis identical with that of a disc lesion, and they may also have pain on hyperextension and lateral flexion toward the painful side as these motions force the subluxated joint. The main distinguishing feature is the pain on passive flexion and more particularly on rotation.

3. The mechanically unstable back. Instability of the bony structure of the spine due to congenital defect, spondylolisthesis, etc., aggravated by faulty posture, obesity, and acute or chronic trauma often leads to recurrent low back and leg pain. There is usually limitation of motion in all directions in the affected area of the spine. With age, the symptoms become arthritic in character. Attacks are usually relieved by rest, external support, and restoration of muscle tone.

4. Arthritis. Specific and nonspecific inflammation of one or more joints of the spine and pelvis, Pott's disease, and early Marie-Struempell arthritis may, on superficial examination, be confused with a herniation of the intervertebral disc. General physical examination and laboratory data will help to differentiate these cases.

5. Sciatic neuritis. A toxic neuritis, usually associated with an inflammatory process elsewhere in the body, has frequently been observed. These cases present extreme unilateral pain and limitation of straight leg raising. Ankle jerks may be absent, and paresthesia present. Such a lesion is differentiated on the basis of normal mobility of the lumbar spine and opposite extremity.

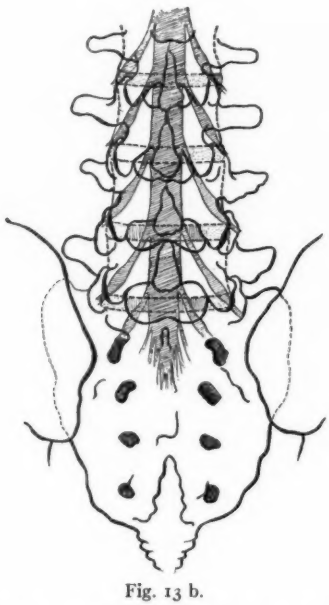


Fig. 13 b.

6. Postural low back pain. The syndromes described by Kindall and Hudson are common clinical entities. Advanced cases may present a history and symptomatology similar to that of a disc lesion. They may be differentiated by an analysis of the postural deformity and the detection of fixed muscle contractures.

TREATMENT

Conservative. We agree with others (1) that not all cases of disc protrusion warrant laminectomy. The readily reducible fluid type of herniation which has not ruptured through the joint capsule and which becomes painless after rest in bed should be treated by conservative means if possible. Undoubtedly, it is this type of lesion which has responded to spine fusion in the past.

Operative. Once the diagnosis of a disc protrusion has been made, the indications for operation are any of the following: (1) pain—unrelieved by usual conservative measures; (2) severe fixed spinal deformity; (3) profound neurological disturbance.

The operation consists of removal of the herniated mass and any sequestrated material within the disc. The extradural approach is used unless an intradural lesion is suspected and, in the majority of cases, this can be accomplished with little

or no removal of bone. Occasionally, it may be necessary to perform a hemilaminectomy, or to remove one of the posterior articulations to expose a laterally placed lesion.

SUMMARY

It is obvious from the literature on the subject that herniation of an intervertebral disc in the lumbar region is a common cause of low back and sciatic pain. There is, however, a dissension of opinion in regard to diagnosis and treatment which is due largely to the inadequacy of presently accepted diagnostic methods and an incomplete understanding of the lesion itself and its pathological sequences.

We have greatly increased our diagnostic accuracy by a return to the fundamentals of orthopedic examination, namely, the study of posture and joint mobility, and by the application of the x-ray to the study of mobility and posture (known as bending films). A clinical syndrome is described which will differentiate the condition from other disorders affecting the lumbosacral spine.

Three types of lesions have been distinguished, a "fluid" or reducible type, a sequestrated type, and a third or fixed type which probably represents an end stage in the process. A trial of conservative therapy is recommended, and indications for operation are stated.

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EDITORIALS

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WHIPPLE'S DISEASE

IN 1907 Whipple[1] described a disease which was "characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues," and which he termed *intestinal lipodystrophy*. This disorder caused loss of weight to the point of emaciation; loss of strength; microcytic anemia; recurrent arthritis; doughy swelling of the abdomen associated with tenderness and gaseous distention; abdominal pain and fatty diarrhea with an average of three or four stools a day which were light or clay colored and consisted of over 50 per cent fat and fatty acids by weight. There was no interference with fat splitting for the fat in the stool was almost completely composed of split fat and soaps in crystalline form.

This disease is rare but should be recognized when encountered for otherwise an erroneous prognosis may be given. The symptoms of abdominal pain often in the right upper quadrant associated with vomiting, gas, and intolerance to fats may suggest gall stones. The abdominal distention, cramp-like pain, vomiting, and x-ray changes in the intestinal pattern may lead to a diagnosis of partial intestinal obstruction. Tuberculosis may be thought of because of the emaciation, loss of appetite, "doughy" consistency of the abdomen, and diarrhea. Carcinomatosis may be considered from the finding of palpable nodules in the abdomen associated with anemia and emaciation. The operative findings may also be confusing. When the abdomen is opened the viscera are seen to be matted together in one solid mass. After the adhesions are freed the loops of intestine appear bound together by a colloid substance but when they are separated a viscous fluid is released which is not gelatinous. The intestinal loops are red, granular, covered with a shaggy exudate and in some locations spotted with small white nodules resembling tubercles. The mesenteric lymph nodes may be greatly enlarged and prominent. Scattered throughout the peritoneal cavity, in the liver, and on the intestines, omentum, and parietal peritoneum are hard, pale pink, nodules that appear typical of carcinomatous implants. However, when these are cut they are found to be thick walled cysts with a central cavity containing a yellow oily substance. This differentiates the condition from pseudomyxoma peritoneii or colloid carcinomatosis which, at first glance, are suggested.

The pathological changes as originally described by Whipple may be summarized as follows: The epithelium of the intestinal mucosa is normal, the villi of the small intestine are enlarged by deposits of neutral fats and fatty acids while the submucosa shows invasion with polyblastic cells about fatty de-

[1]Whipple, G. H., Bull. Johns Hopkins Hosp., 1907, 18: 382.

posits. Wherever it is found, the fat may be present in a variety of forms from minute grains to huge irregular droplets containing rosettes of fatty acid crystals. The majority of the larger deposits are outlined by polyblasts—large mononuclear ameboid cells with pink granular protoplasm and by foam cells with a pale vesicular nucleus. These are most conspicuous in the mesenteric glands in which progressive changes occur, the final stage being "a very large gland packed with fat deposits of all sizes and shapes whose stroma is made up of dense fibrous tissue full of ecchymoses and great numbers of giant and mononuclear cells."

Recently, an opportunity was presented to study this disease in a patient having the diagnosis made from material removed at abdominal exploration. The concept of Whipple that the disorder was due to malabsorption of fat without interference with fat splitting was confirmed. Study of the formed elements of the blood, glucose tolerance, serum protein, and minerals showed them to be normal. The level of phospholipid, cholesterol, and total lipids in the blood was not unusual. There was 59.5 per cent of lipid in the dry stool of which the greater part was split fat. Vitamin A absorption was greatly reduced. The oily substance found in the center of the intra-abdominal nodules contained 74 per cent fatty acid. Apparently, these nodules result from a fibroplastic reaction around fat that is liberated within the peritoneal cavity. The malabsorption and abnormal liberation of fat suggested a fault in the bile and so led to a trial of bile salt medication.

It was found that with adequate dosage of bile salts the symptoms disappear, appetite and strength return, weight is gained, vitamin A absorption improves and the fat content of the stool approaches normal. The symptoms return if the bile salt administration is stopped and are relieved with resumption of treatment. This suggests a fault in bile salt metabolism either by deficient production or from abnormal loss of the bile salts. Lack of suitable analytical methods prevents proof of this theory of the cause of the disease but for the present, at least, this concept gives a satisfactory method of its treatment.

HERMAN E. PEARSE.

MENINGITIS IN HEAD INJURIES

MENINGITIS follows trauma to the head in only a relatively small proportion of cases. Munro gives the rate of occurrence as 1.3 per cent. In 2,740 cases of head injury treated on the neurosurgical service at the Cook County Hospital during 1939 and 1940 meningitis occurred in sixteen cases—0.58 per cent. In spite of its relative infrequency, meningitis accounts for from 3 to 8 per cent of the deaths from head injury. In the group of cases referred to above there were 361 deaths, 10 or 2.8 per cent of which were due to meningitis. Vance, reporting on 507 necropsies in patients dying from head injury, found 41, 8.1 per cent, to be due to meningitis. In only 2 of these cases did meningitis follow compound fracture of the vault of the skull; the rest followed basal skull fracture. This is probably a correct ratio as far as civil practice is concerned. Of course, in war wounds the percentage of cases due to compound fracture will be much higher. Cairns recently reported 24 cases of gunshot wounds of the head with 2 cases of purulent meningitis and 2 other cases of epidural abscess with associated meningitis.

Munro states that the staphylococcus is the most frequent infecting organism, streptococcus next, then pneumococcus, and finally the influenza bacillus. Other writers emphasize the importance of the streptococcus

and pneumococcus. Five of 11 recent cases in the writer's experience were due to pneumococcus. Clark reported 4 cases of meningococcus meningitis from Bellevue and 16 more from the literature that had followed basal skull fracture. It is probable that these individuals harbored the meningococcus in their nasopharynx and the basal skull fracture provided an avenue for entry of the organisms into the intracranial cavity. Gross and Ehrlich emphasized the danger of fracture of the petrous portion of the temporal bone in the presence of acute or chronic otitis media or mastoiditis. Cases of otorrhea and rhinorrhea have long been recognized as likely to develop meningitis, and rhinorrhea justly has the worst reputation in this respect.

Meningitis following head injury may be divided into two groups: fulminating and delayed. In the latter, symptoms do not appear for several days or longer after the injury and the patient seems to be well out of danger, at least as far as infection is concerned. The symptoms of meningitis following head injury are similiar to those of meningitis due to other causes. Headaches, vomiting, fever, photophobia, delirium, stupor, incontinence, stiff neck, and a positive Kernig sign are the most common symptoms. Since many or all of these symptoms can be due to brain injury, especially if associated with subarachnoid bleeding, it is therefore necessary to do a spinal puncture if there is any suspicion of meningitis. The spinal fluid is typically under high pressure and cloudy with a marked pleocytosis with polymorphonuclear leucocytes. The total protein is increased and the sugar and chloride content are lowered. Cultures reveal the offending organism. Often the spinal fluid is blood tinged or frankly bloody due to subarachnoid hemorrhage. Differential cell count may then be of some value, but diagnosis depends on the results of culture.

In the past, mortality has ranged from 80 to 100 per cent, being considerably nearer the latter figure in proved cases. Because of this high mortality a number of procedures have been tried by various surgeons. Among these are frequent or continuous spinal drainage, laminectomy or suboccipital craniectomy with continuous drainage of fluid, and intracarotid injections of antisera or antiseptic solutions. The advent of sulfonamide therapy has materially altered the possibility for cure in all types of purulent meningitis. Grant has stated that the mortality for posttraumatic meningitis should be lowered to 25 per cent. Some writers have advised the prophylactic administration of sulfanilamide in cases of compound fracture or of drainage of cerebrospinal fluid to the exterior. Gurdjian advises against it. He reported 3 cases of posttraumatic meningitis that recovered on sulfanilamide therapy. Two of these were due to hemolytic streptococci; cultures of the spinal fluid were negative in the other. In all 3 the condition was recognized early.

General prophylactic measures are very important in cases of scalp laceration, compound fracture, bleeding from ears or nose, pneumocephalus, and otorrhea or rhinorrhea. Thorough and meticulous débridement of all wounds involving scalp and bone should be carried out with excision of contaminated and devitalized tissue. If the dura is penetrated the cerebral wound should be débrided by appropriate neurosurgical methods—using suction and irrigation. If foreign bodies are present they should be removed unless that would entail damage to uninjured cerebral structures. These are major neurosurgical procedures and must be postponed until the condition of the patient permits and the proper operative conditions can be attained. However, the sooner it is done after the injury the better, but good results can be obtained

when operative procedures have been delayed as long as 72 to 96 hours. In such cases the preoperative and postoperative prophylactic administration of sulfonamides is of value but must never be substituted for proper surgical treatment. Primary closure of these wounds is usually advisable.

Patients with bleeding or drainage of cerebrospinal fluid from ear or nose should be kept flat in bed. There must be no interference with the drainage and irrigations are strictly contradicted. Drainage of cerebrospinal fluid from the ear almost always stops spontaneously within 48 hours; drainage from the nose usually does so. If it does not do so within 72 hours plastic closure of the dural defect should be undertaken through a transfrontal craniotomy, the condition of the patient permitting. This should only be undertaken by a competent surgeon under proper operating conditions.

Cases of fracture involving the frontal sinus with or without external compounding of the wound should be operated on as other cases of compound fracture. They are otherwise likely to develop pneumocephalus and meningitis is very likely to follow.

If symptoms of meningitis appear in a patient that has had a head injury, spinal puncture should be done at once. If there is a pleocytosis, sulfonamide therapy should be begun without delay. Sulfanilamide may be given until the organism has been identified. If the infection is due to a pneumococcus, the organism should be typed and appropriate antisera if available should be given. Sulfapyridine should be given in such cases. Daily blood levels of the sulfonamide used should be determined, and a blood count should be done daily. The new drug sulfadiazine may prove of value in meningitis. Lumbar puncture should be performed every one to three days until the cell count is normal and cultures are sterile. The sugar and chloride content will approach normal as the infection clears and therapy should be continued for several days after the patient has clinically recovered and the cerebrospinal fluid findings are normal. Only by early and intensive treatment can we hope to approach the goal of a 25 per cent mortality which was set by Grant.

Supportive measures of a high fluid and caloric intake, adequate sedation, and blood or plasma transfusions as indicated, must not be neglected. If a patient is comatose or incontinent, the special nursing care that such cases require must be furnished. The recoveries now reported in the literature indicate that posttraumatic meningitis no longer presents a hopeless prognosis but rather a clear cut challenge to the surgeon to make an early diagnosis and institute appropriate treatment.

HAROLD C. VORIS.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

IN Doctor Gorsch's *Perineopelvic Anatomy*[1] the proctologist is presented with a textbook of a distinctly modern type, its publication virtually coinciding with the recognition of anorectal surgery as a full fledged specialty.

The work is one of a fundamental nature, being concerned with the structure of the canal and of its supporting elements, rather than with surgical methods by which the normal relations of the parts may be restored. In his preface to the reader Dr. Gorsch points out that fundamental training for the specialist is rarely offered by the standard textbooks of gross anatomy, less frequently arranged for in the curriculum of the regular medical school. These circumstances are an invitation to competent practitioners, either alone or in collaboration with anatomists, to prepare instructional volumes for the use of aspirants in gynecology, proctology, thoracic surgery, etc.

The text presents the anatomy of the anal canal, the mucosal and submucosal structures; intrinsic anorectal musculature; the pelvic and urogenital layers and associated spaces; and the nerves and vessels of supply. Of the original figures, some forty are simple diagrams; equal in number are photographs of dissections and sections (the latter gross and microscopic). The author uses an even larger number of borrowed figures from textbooks and journal articles, divided about equally between diagrammatic and detailed drawings. Some of the diagrams are very instructive, but would be more serviceable were they accompanied by drawings, from actual dissections, of the same set of structures. The use of photographs of dissections is not altogether fortunate, since such pictorial records are, in the present state of this mechanicochemical science, somewhat baffling—the registered lights, shadows, and depths being unfamiliar to the reader. There is no substitute for the genius of the skilled anatomical artist.

The account of the diaphragmatic supports seems rather inconclusive. The description of the vessels and nerves could be improved by a discussion of the more common variations in branching. Some of the variations in arterial pattern are so profound that a knowledge of their existence would be useful to the gynecologist.

The long list of pelvic "spaces" serves to make the anatomy of the subserous connective tissue rather forbidding, even to the well informed reader. New names are offered when established ones are simpler, more descriptive and universally understood. In recent years, through the efforts of the Basle Commission, thousands of unnecessary synonyms have been dropped from anatomic nomenclature; it would seem unwise to drag back, into the anatomical workshop, superfluous verbal tools which are no better than those recently discarded by a highly intelligent commission.

BARRY ANSON.

[1] PERINEOPELVIC ANATOMY; FROM THE PROCTOLOGIST'S VIEWPOINT. By R. V. Gorsch, A.B., M.D. New York: The Tilghman Co., 1941.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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